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FILE 'USPAT2' ENTERED AT 19:55:43 ON 14 DEC 2008
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=> s gentian violet
L1         6394 GENTIAN VIOLET

=> s glycerin s water
L2            0 GLYCERIN S WATER

=> s glycerin and water
L3       105578 GLYCERIN AND WATER

=> s pad or bandage or gauze or sponge or surgical
L4      3647596 PAD OR BANDAGE OR GAUZE OR SPONGE OR SURGICAL

=> s l1 and l3
L5          252 L1 AND L3

=> s l4 and l5
L6          133 L4 AND L5

=> s polyurethane
L7       494947 POLYURETHANE

=> s l6 and l7
L8           41 L6 AND L7

=> dup rem
ENTER L# LIST OR (END):l8
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2,
IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML, USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L8
L9            37 DUP REM L8 (4 DUPLICATES REMOVED)

=> s pressure sensitive adhesive
L10       74625 PRESSURE SENSITIVE ADHESIVE

=> s l9 and l10

L11          10 L9 AND L10

=> d 111 1-10 ibib, kwic

L11  ANSWER 1 OF 10  IFIPAT  COPYRIGHT 2008 IFI on STN
AN                          11113820  IFIPAT;IFIUDB;IFICDB
TITLE:                      Medical pad, and method for making and
                            using
INVENTOR(S):                White; Daniel A., La Grange, TX, US
                            McAllister; Theodore, San Antonio, TX, US
                            Simonson; Richard M., New York, NY, US
                            Suchanec; Richard R., Newark, DE, US
PATENT ASSIGNEE(S):         Unassigned
PATENT ASSIGNEE PROBABLE: general Wound Kare Inc (Probable)
AGENT:                      William H Holt;Law Offices, 12311 Harbor Drive,
                            Woodbridge, VA, 22192, US

                               NUMBER          PK     DATE
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PATENT INFORMATION:	US 20060062829	A1	20060323
APPLICATION INFORMATION:	US 2003-525323		20030820
	WO 2003-US25897		20030820
			20050920 PCT 371 date
			20050920 PCT 102(e) date

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2002-404404P	20020820 (Provisional)
	US 2003-451682P	20030305 (Provisional)
FAMILY INFORMATION:	US 20060062829	20060323

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION
ENTRY DATE: Entered STN: 24 Mar 2006
Last Updated on STN: 24 Mar 2006

NUMBER OF CLAIMS: 10

TI Medical pad, and method for making and using

AB A germicidal absorptive material for use in surgical packings, wound bandages, sanitary tampons and bed sore prevention and/or treatment uses is provided by a foam-like matrix of hydrophilic polyurethane polymer to which application-specific loads of a germicidal disinfectant dye have been made. Polyurethane polymer of various densities and thicknesses exhibits an exceptional ability to absorb different levels of a number of disinfectant dyes, both basic and acidic, such as gentian violet and methylene blue, respectively. The relationship between dye-load and application-specific uses permits a totally-bound gentian violet pad to be used as a conventional bandage or pad on a surface wound with the capability of preventing the incursion of external pathogens from entering the wound through the pad, where the pathogens are killed by the bound-dye. The wound exudate is absorbed safely by the pad, where wound-originating pathogens are also killed. When the loaded dye's concentration is saturated by exceeding the bounddye limit, the limited. . . . to be delivered to the wound, particularly deep wounds, to rapidly kill pathogens in the wound. The free dye delivery pad can then be replaced by the bound-dye pad to absorb the wound exudate.

ACLM 2. The process in claim 1, wherein of excess of non-bound dye is left in the sponge, which is then dried to provide a delivery system for non-bound, free dye to an open wound.
3. The process in claim 1, wherein the disinfectant dye is dissolved into water a 15:1 water to glycerin mixed solvent.
4. The process in claim 1, wherein the disinfectant dye is selected from the group consisting of gentian violet, brilliant green, malachite green, methyl blue, methylene blue, acridine orange, acridine yellow, quinacrine, trypan blue, and trypan red.
5. The process in claim 1, wherein the disinfectant dye comprises a mixture of gentian violet, glycerin and water.
6. The process in claim 5, wherein said mixture is comprised of eight drops of gentian violet of one-percent strength,
7. The process in claim 1, wherein said sponge with bound dye is provided with a transparent backing film bonded to the sponge with a pressure sensitive adhesive (PSA) with water-impervious polyethylene for "bedsore" sheeting.
8. A medical pad including medicaments for treating, protecting

and healing wounds, said pad being in the form of a foam sponge material constructed from polyurethane and having hydrophilic properties, said pad having been treated with a solution comprised of a medicament, and a solvent therefor.
9. A medical pad as defined in claim 8 wherein said medicament is comprised of gentian violet having a strength in the range of 1 to 3 percent.
10. A medical pad as defined in claim 9 wherein said pad has been exposed to a solution of said gentian violet, glycerin and water.

ECLM 1. A process for making an antimicrobial, absorbent material including the steps of submerging a hydrophilic polyurethane sponge into a solution of disinfectant dye capable of being bound to the sponge to varying degrees; squeezing the entrained air bubbles out of the voids while submerged to maximize solution and dye incorporation; and drying the sponge to form an antimicrobial absorbent pad.

L11 ANSWER 2 OF 10 USPATFULL on STN

ACCESSION NUMBER:	2006:110717 USPATFULL
TITLE:	Hydroxide-releasing agents as skin permeation enhancers
INVENTOR(S):	Luo, Eric C., Plano, TX, UNITED STATES Jacobson, Eric C., San Diego, CA, UNITED STATES Hsu, Tsung-Min, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20060093659	A1	20060504
APPLICATION INFO.:	US 2005-303614	A1	20051216 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2003-371352, filed on 19 Feb 2003, ABANDONED Division of Ser. No. US 2000-738410, filed on 14 Dec 2000, GRANTED, Pat. No. US 6586000 Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, ABANDONED

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	INTELLECTUAL PROPERTY GROUP, FREDRIKSON & BYRON, P.A., 200 SOUTH SIXTH STREET, SUITE 4000, MINNEAPOLIS, MN, 55402, US
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1-58
NUMBER OF DRAWINGS:	14 Drawing Page(s)
LINE COUNT:	3425

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . . the hydroxide-releasing agent prior to transdermal drug administration. Such a solution will generally be comprised of a protic solvent (e.g., water or alcohol) and have a pH in the range of about 8.0 to 13, preferably 8.0 to 11.5, more preferably. . .

SUMM . . . surface or may involve use of a drug delivery device. In either case, it is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus enhance the flux of the active agent through the patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD The term "aqueous" refers to a formulation or drug delivery system that contains water or that becomes water-containing

following application to the skin or mucosal tissue.

DETD . . . fluid may be natural moisture at the skin surface, or a patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine, . . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water must be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus enhance the flux of the active agent through the patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD . . . Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy. . .

DETD Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and

ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . side facing the receiver solution. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the concentration of estradiol in the. . .

DETD . . . the patch was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added; the liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

Estradiol	0.0313 g (0.5%)		0.0322 g (0.5%)	0.0308 g (0.5%)
NaOH	0		0.0155 g (0.3%)	0.025 g (0.4%)
DI water	0		0.4155 g (6.9%)	0.425 g (7.0%)
PIB* adhesive (30% solid)	4 g (66.3%)		4 g (66.0%)	4 g (65.8%). . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

1.2 g (16.7%)		1.2 g (15.8%)	1.2 g (15.7%)	(15.7%)
NaOH	0	0.19 g (2.5%)	0.215 g (2.8%)	0.225 g (2.9%)
DI water	0	0.19 g (2.5%)	0.215 g (2.8%)	0.225 g (2.9%)

PIB adhesive (30% solid). . . 4 g 4 g 4 g 4 g

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD The cells were filled with DI water. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . . 0.75 g 0.75 g

	(8.5%)	(8.2%)	(8.1%)	(8.1%)
NaOH	0	0.165 g (1.8%)	0.195 g (2.1%)	0.23 g (2.5%)
DI water	1.1 g (12.4%)	1.265 g (13.8%)	1.295 g (14.0%)	1.33 g (14.3%)
Propylene glycol	0.5 g	0.5 g	0.5 g. . .	

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was cut. . .

DETD . . . 2.4 g

	(14.0%)	(14.0%)	(13.9%)	(13.8%)
NaOH	0.6 g (3.5%)	0.65 g (3.8%)	0.69 g (4.0%)	0.73 g (4.2%)
DI water	0.6 g (3.5%)	0.65 g (3.8%)	0.69 g (4.0%)	0.73 g (4.2%)
PIB adhesive (30%	8 g	8 g	8. . .	

DETD . . . g 0.135 g 0.15 g

	(6.2%)	(7.1%)	(7.8%)
Ethanol	0.4 g (24.5%)	0.4 g (21.5%)	0.4 g (21.1%)	0.4 g (20.7%)
DI Water	0.6 g (36.8%)	0.715 g (38.4%)	0.735 g (38.7%)	0.75 g (38.9%)
HPMCP*	0.03 g	0.03 g	0.03 g	0.03 g

. . .

DETD . . . g 0.5 g 0.5 g

	(6.7%)	(5.7%)	(5.6%)	(5.5%)
Na.sub.2CO.sub.3 0		0.29 g (3.3%)	0.44 g (5.0%)	0.74 g (8.1%)
DI water	1.0 g (13.5%)	2.0 g (23.0%)	2.0 g (22.6%)	2.0 g (21.9%)
Methyl	0.5 g	0.5 g	0.5 g	0.5. . .

DETD . . . g 0.5 g 0.5 g

	(6.6%)	(6.1%)	(6.1%)	(6.1%)
K.sub.3PO.sub.4 0		0.57 g (7.0%)	0.6 g (7.3%)	0.66 g (8.0%)
DI water	1.0 g (13.2%)	1.0 g (12.2%)	1.0 g (12.2%)	1.0 g (12.1%)
Propylene	0.5 g	0.5 g	0.5 g	0.5. . .

DETD . . . 0.5 g 5 g

	(6.9%)	(6.4%)	(6.3%)	(6.1%)
K.sub.3PO.sub.4 0		0.57 g (7.3%)	0.73 g (9.2%)	1.05 g (12.7%)
DI water	1.0 g (13.9%)	1.0 g (12.9%)	1.0 g (12.6%)	1.0 g (12.1%)
Methyl	0.5 g	0.5 g	0.5 g	0.5. . .

DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of

water on the top of the skin was reduced. The pH of the PPA-HCl patch measured using the procedures listed above. . .

DETD . . . g	0.5 g	0.5 g		
alcohol	(8.0%)	(7.8%)	(7.6%)	(7.4%)
K.sub.3PO.sub.4 0		0.1 g	0.3 g	0.48 g
		(1.6%)	(4.6%)	(7.1%)
DI water	0.5 g	0.5 g	0.5 g	0.5 g
	(8.0%)	(7.8%)	(7.6%)	(7.4%)
Propylene	0.25 g	0.25 g	0.25 g	0.25 g. . .

DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the estradiol patch measured using the procedures listed above. . .

DETD . . . 0.03 g	0.03 g			
	(0.5%)	(0.4%)	(0.4%)	(0.4%)
Na.sub.2CO.sub.3 0		0.11 g	0.3 g	0.45 g
		(1.6%)	(4.1%)	(6.1%)
DI water	0.5 g	1.2 g	1.2 g	1.2 g
	(8.0%)	(16.9%)	(16.5%)	(16.2%)
Methyl	0.5 g	0.5 g	0.5 g	0.5. . .

DETD . . . and 34). This behavior may be because the amount of Na.sub.2CO.sub.3 that could be dissolved by the small amount of water on the top of the skin remained about the same for Est-PC2, Est-PC3 and Est-PC4. The pH of the estradiol. . .

DETD . . . 0.03 g	0.03 g	0.03 g		
	(0.5%)	(0.4%)	(0.4%)	(0.4%)
MgO	0	0.11 g	0.3 g	0.45 g
		(1.6%)	(4.1%)	(6.1%)
DI water	0.5 g	1.2 g	1.2 g	1.2 g
	(8.0%)	(16.9%)	(16.5%)	(16.2%)
Methyl alcohol. . .	0.5 g	0.5 g	0.5 g	0.5 g

DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the estradiol patch measured using the procedures listed above. . .

DETD . . . 0.5 g	0.5 g	0.5 g (5.7%)		
	(6.9%)	(6.0%)	(5.9%)	
MgO	0	0.11 g	0.26 g	0.50 g (5.7%)
		(1.3%)	(3.1%)	
DI water (22.9%)	1.0 g	2.0 g	2.0 g	2.0 g
	(13.9%)	(24.0%)	(23.6%)	
Methyl	0.5 g	0.5 g	0.5 g	0.5 g. . .

DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the PPA-HCl patch measured using the procedures listed above. . .

DETD . . . cells were used for each test group for a total of 18 cells. The cells were filled with deionized (DI) water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography) to. . . Leuprolide Transdermal Solutions

	Leu-S1	Leu-S2*	Leu-S3*
Leuprolide	0.003 g	6.4 + 10.sup.-4 g	6.4 g + 10.sup.-4 g
	(0.4%)	(0.18%)	(0.16%)
DI water	0.45 g	0.28 g (80.9%)	0.33 g (80.3%)

	(64.0%)		
NaOH	0 g	0.0125 g (3.6%)	0.0275 g (6.7%)
	(0.0%)		
Propylene	0.25 g. . .	(35.6%)	

*Solutions Leu-S2 and Leu-3 were prepared using 0.15 g of Leu-S1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.

DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . . 45. Once the oxytocin solution is applied, the donor chamber was covered with parafilm. The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . . each time point, which were listed in Table 46.

TABLE 45

Formulation for the Oxytocin Solution

Oxytocin	0.005 g
DI water	0.6 g
Propylene Glycol	0.6 g

DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . . 47. Once the oxytocin solution is applied, the donor chamber was covered with parafilm. The cells were filled with DI water as a receiver solution. The DI water has been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of oxytocin in the receiver. . . each time point, which were listed in Table 48.

TABLE 47

Formulation for the Oxytocin Solution

Oxytocin	0.005 g
DI water	0.6 g
Propylene Glycol	0.6 g

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . side facing the receiver solution. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration

of diclofenac sodium in. . .

DETD . . . of the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water /patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . 4 g 4 g solid)

	(61.5%)	(60.9%)	(60.6%)	(59.7%)
Heptane	1 g	1 g	1 g	1 g
	(15.4%)	(15.2%)	(15.2%)	(14.9%)
DI water	0	0.035 g	0.05 g	0.1 g
		(0.5%)	(0.8%)	(1.5%)

DETD . . . cell with the stratum corneum side facing the donor solution. Three diffusion cells were used for each formulation. l0% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . . glycol (28.2%)

	(27.6%)	(27.4%)	(26.9%)	
Ethyl alcohol	1 g	1 g	1 g	1 g
	(46.9%)	(46.1%)	(45.7%)	(44.8%)
DI water	0.2 g	0.22 g	0.23 g	0.25 g
	(9.4%)	(10.1%)	(10.5%)	(11.2%)
HPMC	0.03 g	0.03 g	00.3 g	0.03. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . side facing the receiver solution. Three diffusion cells were used for each formulation. The cells were filled with l0% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . .

DETD . . . the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water /patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . g 0.5 g 0.5 g

glycol	(7.9%)	(7.9%)	(7.8%)	(7.8%)
NaOH	0	0.02 g	0.04 g	0.075 g
		(0.3%)	(0.6%)	(1.2%)
DI water	0	0.02 g	0.04 g	0.075 g
		(0.3%)	(0.6%)	(1.2%)
PIB adhesive	4 g	4 g	4 g	4 g

(30%. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken

were analyzed by an HPLC for the concentration of oxybutynin HCl in. . . Solution Weight) for Three Oxybutynin HCl Transdermal Systems

	Oxy-P1	Oxy-P2	Oxy-P3
Oxybutynin HCl	0.5 g (6.5%)	0.5 g (6.3%)	0.5 g (6.2%)
DI water (10.5%)	0.65 g (8.4%)	0.75 g (9.5%)	0.85 g
NaOH	0.15 g (1.9%)	0.25 g (3.2%)	0.35 g (4.3%)
Propylene glycol	0.3. . .		

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . . interface were listed in Table 65. For all other cells, the receiving fluid was completely withdrawn and replaced with fresh ethanol/water solution. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in the receiver solution. The. . .

DETD . . . the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . g 4 g

(30% solid)	(61.5%)	(61.3%)	(61.2%)	(60.6%)
Heptane	1 g	1 g	1 g	1 g
	(15.4%)	(15.3%)	(15.3%)	(15.2%)
DI water	0	0.01 g	0.02 g	0.05 g
		(0.2%)	(0.3%)	(0.8%)

CLM What is claimed is:

65. The composition of claim 6 wherein the polymeric matrix comprises a pressure-sensitive adhesive selected from the group consisting of polyethylenes; polysiloxanes; polyisobutylenes; polyacrylates; polyacrylamides; polyurethanes; plasticized ethylene-vinyl acetate copolymers; and tacky rubbers such. . .

CLM What is claimed is:

71. The composition of claim 70 wherein the polymeric matrix comprises a pressure-sensitive adhesive selected from the group consisting of polyethylenes; polysiloxanes; polyisobutylenes; polyacrylates; polyacrylamides; polyurethanes; plasticized ethylene-vinyl acetate copolymers; and tacky rubbers such. . .

L11 ANSWER 3 OF 10 USPATFULL on STN

ACCESSION NUMBER: 2005:87025 USPATFULL

TITLE: Transdermal and topical administration of drugs using basic permeation enhancers

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20050074487	A1	20050407
APPLICATION INFO.:	US 2004-863432	A1	20040607 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-176952, filed on 21 Jun 2002, ABANDONED Continuation-in-part of Ser. No. US 2003-675603, filed on 29 Sep 2003, PENDING Division of Ser. No. US 2002-176265, filed on 19 Jun 2002, GRANTED, Pat. No. US 6673363 Continuation-in-part of Ser. No. US 2002-175769, filed on 19 Jun 2002, ABANDONED Continuation-in-part of Ser. No. US 2002-175721, filed on 19 Jun 2002, ABANDONED Continuation-in-part of Ser. No. US 2002-175682, filed on 19 Jun 2002, PENDING Continuation-in-part of Ser. No. US 2002-176264, filed on 19 Jun 2002, PENDING Continuation-in-part of Ser. No. US 2002-175681, filed on 19 Jun 2002, PENDING Continuation-in-part of Ser. No. US 2001-972008, filed on 4 Oct 2001, GRANTED, Pat. No. US 6582724 Continuation-in-part of Ser. No. US 2000-738410, filed on 14 Dec 2000, GRANTED, Pat. No. US 6586000 Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-738395, filed on 14 Dec 2000, GRANTED, Pat. No. US 6719997 Continuation-in-part of Ser. No. US 2000-607892, filed on 30 Jun 2000, ABANDONED

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED INTELLECTUAL PROPERTY LAW GROUP, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 52
EXEMPLARY CLAIM: 1
LINE COUNT: 4435

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0017] The term "aqueous" refers to a composition, formulation or drug delivery system that contains water or that becomes water-containing following application to the skin or mucosal tissue.

DETD [0018] The term "base" is used in its traditional sense, i.e., a substance that dissolves in water to produce hydroxide ions. The water is typically an aqueous fluid, and may be natural moisture at the skin surface, or the patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . ointments, etc., may experience a net loss of moisture after being applied to the body surface, i.e., the amount of water lost is greater than the amount of water received from the body surface. In that case, the pH of the formulation may be different than its pH when. . .

DETD . . . N)

Sodium hydroxide.sup.1,2,3	14 (5%), 13 (0.5%), 12 (0.05%)
Potassium hydroxide.sup.1,2,3	13.5 (0.1 M)
Calcium hydroxide.sup.1,3	12.4 (saturated solution in water)
Magnesium hydroxide.sup.1,3	9.5 to 10.5 slurry
Magnesium oxide.sup.1,2,3	10.3 (saturated aqueous solution)

	Calcium oxide.sup.3	Soluble in water, Form Ca(OH).sub.2
	Sodium acetate.sup.1,3	.about.8.9 (0.1 N)
	Sodium acetate, trihydrate.sup.1,2	8.9 (0.1 N)
	Sodium acetate, anhydrous.sup.1,2	.about.8.9 (0.1 N)

Sodium. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water is preferably present in order for the hydroxide ions to be provided by the base, and thus enhance the flux. . . the active agent through the patient's body surface. Thus, such a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive backing layer so that moisture evaporating from the body. . .

DETD . . . Pharmacy, 20.sup.th edition (Lippincott Williams & Wilkins, 2000), ointment foundations may be grouped in four classes: oleaginous, emulsifiable, emulsion, and water-soluble. Oleaginous ointment foundations include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment foundations, also known as absorbent ointment foundations, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment foundations are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment foundations are prepared from polyethylene glycols of varying molecular weight.

DETD [0241] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream foundations are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . acceptable chemicals to buffer, stabilize or preserve the

solute. Commonly used examples of solvents used in preparing solutions are ethanol, water, propylene glycol or any other pharmaceutically acceptable vehicle.

DETD . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . of the patches was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added. The liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

DETD . . . g (wt %) g (wt %) g (wt %)

Estradiol	0.0313	(0.5)	0.0322	(0.5)	0.0308	(0.5)
NaOH	0		0.0155	(0.3)	0.025	(0.4)
DI water	0		0.4155	(6.9)	0.425	(7.0)
PIB adhesive (30% solid)	4	(66.3)	4	(66.0)	4	(65.8)
Methylal	1.8	(29.8)	1.4	(23.1)	1.4	(23.0)
Ethanol	0.2. . .					

DETD . . . in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with a 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the concentration of estradiol in the. . .

DETD . . . (wt %) g (wt %)

Ketoprofen	1.2	(16.7)	1.2	(15.8)	1.2	(15.7) 1.2

(15.7)
NaOH 0 0.19 (2.5) 0.215 (2.8) 0.225
(2.9)
DI water 0 0.19 (2.5) 0.215 (2.8)
0.225 (2.9)
PIB adhesive 4 (55.6) 4 (52.8) 4 (52.4) 4
(52.3)
(30% solid)
Methylal 2 (27.8) 2. . .
DETD . . . (wt %) g (wt %)

PPA-HCl 0.75 (8.5) 0.75 (8.2) 0.75 (8.1) 0.75
(8.1)
NaOH 0 0.165 (1.8) 0.195 (2.1) 0.23
(2.5)
DI water 1.1 (12.4) 1.265 (13.8) 1.295 (14.0)
1.33 (14.3)
PG 0.5 (5.6) 0.5 (5.4) 0.5 (5.4) 0.5
(5.4)
Methylal 1 (11.3) 1 (10.9). . .
DETD . . . as described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with DI water . The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . .
DETD . . . %) g (wt %)

Ketoprofen 2.4 (14.0) 2.4 (14.0) 2.4 (13.9) 2.4
(13.8)
NaOH 0.6 (3.5) 0.65 (3.8) 0.69 (4.0) 0.73
(4.2)
DI water 0.6 (3.5) 0.65 (3.8) 0.69 (4.0)
0.73 (4.2)
Tetraglycol 0.5 (2.9) 0.5 (2.9) 0.5 (2.9) 0.5
(2.9)
Isopropyl- 0.4 (2.3) 0.4 (2.3). . .
DETD . . . (32.3) 0.6 (31.6) 0.6 (31.1)
NaOH 0 0.115 (6.2) 0.135 (7.1) 0.15
(7.8)
Ethanol 0.4 (24.5) 0.4 (21.5) 0.4 (21.1) 0.4
(20.7)
DI water 0.6 (36.8) 0.715 (38.4) 0.735 (38.7)
0.75 (38.9)
HPMCP 0.03 (1.8) 0.03 (1.6) 0.03 (1.6) 0.03
(1.6)
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.7) 0.5 (5.7) 0.5 (5.6) 0.5
(5.5)
Na.sub.2CO.sub.3 0 0.29 (3.3) 0.44 (5.0) 0.74
(8.1)
DI water 1.0 (13.5) 2.0 (23.0) 2.0 (22.6)
2.0 (21.9)
Methyl alcohol 0.5 (6.7) 0.5 (5.7) 0.5 (5.6) 0.5
(5.5)
PG 0.2 (2.7) 0.2. . .
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.6) 0.5 (6.1) 0.5 (6.1) 0.5
(6.1)

K.sub.3PO.sub.4 0 0.57 (7.0) 0.6 (7.3) 0.66 (8.0)
DI water 1.0 (13.2) 1.0 (12.2) 1.0 (12.2) 1.0 (12.1)
PG 0.5 (6.6) 0.5 (6.1) 0.5 (6.1) 0.5 (6.1)
Methyl alcohol 0.5 (6.6) 0.5. . .
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.9) 0.5 (6.4) 0.5 (6.3) 0.5 (6.1)
K.sub.3PO.sub.4 0 0.57 (7.3) 0.73 (9.2) 1.05 (12.7)
DI water 1.0 (13.9) 1.0 (12.9) 1.0 (12.6) 1.0 (12.1)
Methyl alcohol 0.5 (6.9) 0.5 (6.4) 0.5 (6.3) 0.5 (6.1)
PG 0.2 (2.8) 0.2. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . 0.03 (0.5) 0.03 (0.4)
Methyl alcohol 0.5 (8.0) 0.5 (7.8) 0.5 (7.6) 0.5 (7.4)
K.sub.3PO.sub.4 0 0.1 (1.6) 0.3 (4.6) 0.48 (7.1)
DI water 0.5 (8.0) 0.5 (7.8) 0.5 (7.6) 0.5 (7.4)
PG 0.25 (4.0) 0.25 (3.9) 0.25 (3.8) 0.25 (3.7)
PIB adhesive 4 (63.7) 4. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . (wt %) g (wt %)

Estradiol 0.03 (0.5) 0.03 (0.4) 0.03 (0.4) 0.03 (0.4)
Na.sub.2CO.sub.3 0 0.11 (1.6) 0.3 (4.1) 0.45 (6.1)
DI water 0.5 (8.0) 1.2 (16.9) 1.2 (16.5) 1.2 (16.2)
Methyl alcohol 0.5 (8.0) 0.5 (7.1) 0.5 (6.9) 0.5 (6.7)
PIB adhesive 4 (63.7). . .
DETD . . . to 23.3%. This behavior may be because the amount of Na.sub.2CO.sub.3 that could be dissolved by the small amount of water on the top of the skin remained about the same for Est-12, Est-13 and Est-14.
DETD . . . (wt %) g (wt %)

Estradiol 0.03 (0.5) 0.03 (0.4) 0.03 (0.4) 0.03 (0.4)
MgO 0 0.11 (1.6) 0.3 (4.1) 0.45 (6.1)
DI water 0.5 (8.0) 1.2 (16.9) 1.2 (16.5) 1.2 (16.2)
Methyl alcohol 0.5 (8.0) 0.5 (7.1) 0.5 (6.9) 0.5 (6.7)
PIB adhesive 4 (63.7). . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . g (wt%) g (wt %)

PPA-HCl 0.5 (6.9) 0.5 (6.0) 0.5 (5.9) 0.5 (5.7)
MgO 0 0.11 (1.3) 0.26 (3.1) 0.50 (5.7)
DI water 1.0 (13.9) 2.0 (24.0) 2.0 (23.6) 2.0 (22.9)

Methyl alcohol 0.5 (6.9) 0.5 (6.0) 0.5 (5.9) 0.5 (5.7)
PG 0.2 (2.8) 0.2. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . Leu-3.sup.*

	g (wt %)	g (wt %)	g (wt %)
Leuprolide	0.003 (0.4) (0.16)	6.4 + 10.sup.-4 (0.18)	6.4 + 10.sup.-4
DI water	0.45 (64.0)	0.28 (80.9)	0.33 (80.3)
NaOH	0	0.0125 (3.6)	0.0275 (6.7)
PG	0.25 (35.6)	0.053 (15.3)	0.053 (13.0)

*Solutions Leu-2 and Leu-3 were prepared using 0.15 g of Leu-1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.
DETD [0368] The cells were filled with DI water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography) to. . .
DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .
DETD . . . was applied, the donor chamber was covered with parafilm.
TABLE 45

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0374] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . .
DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .
DETD . . . is applied, the donor chamber was covered with parafilm.
TABLE 47

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0378] The cells were filled with DI water as a receiver

solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of oxytocin in the receiver. . .

DETD . . . 0.1 (1.5)

PIB adhesive (30% solid)	4 (61.5)	4 (60.9)	4 (60.6)	4 (59.7)
Heptane	1 (15.4)	1 (15.2)	1 (15.2)	1 (14.9)
DI water	0	0.035 (0.5)	0.05 (0.8)	0.1 (1.5)

DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in. . .

DETD . . . (13.7) 0.3 (13.50)

sodium PG	0.6 (28.2)	0.6 (27.6)	0.6 (27.4)	0.6 (26.9)
Ethyl alcohol	1 (46.9)	1 (46.1)	1 (45.7)	1 (44.8)
DI water	0.2 (9.4)	0.22 (10.1)	0.23 (10.5)	0.25 (11.2)
HPMC	0.03 (1.4)	0.03 (1.4)	00.3 (1.4)	0.03 (1.3)
NaOH	0	0.02 (0.9)	0.03. . .	

DETD . . . from these gels was measured as described in Example 6. Three diffusion cells were used for each formulation. 10% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . .

DETD . . . (7.9) 0.5 (7.8) 0.5 (7.8)

PG	0.5 (7.9)	0.5 (7.9)	0.5 (7.8)	0.5 (7.8)
NaOH	0	0.02 (0.3)	0.04 (0.6)	0.075 (1.2)
DI water	0	0.02 (0.3)	0.04 (0.6)	0.075 (1.2)
PIB adhesive (30% solid)	4 (63.5)	4 (63.1)	4 (62.7)	4 (62.0)
Heptane	1 (15.9)	1. . .		

DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . .

DETD . . . 0.05 (0.8)

PIB adhesive (30% solid) (60.6)	4	(61.5)	4	(61.3)	4	(61.2)	4	
Heptane (15.2)	1	(15.4)	1	(15.3)	1	(15.3)	1	
DI water 0.05 (0.8)	0		0.01	(0.2)	0.02	(0.3)		

DETD . . . described in the Methods section. Twelve diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . .

DETD . . . Solution Weight

	Al-1 g (wt %)		Al-2 g (wt %)		Al-3 g (wt %)	
Alendronate sodium	0.30	(3.2)	0.30	(3.2)	0.30	(3.2)
Glycerin	1.00	(10.8)	1.00	(10.6)	1.00	(10.5)

NaOH	0		0.05	(0.5)	0.10	(1.1)
PIB adhesive (30% solid)	7.5	(80.6)	7.5	(79.8)	7.5	(78.9)
Heptane	0.50	(5.4)	0.50	(5.3)	0.50	(5.3)
DI water	0		0.05	(0.5)	0.10	(1.1)

DETD . . . Film Weight

	Al-1 g (wt %)		Al-2 g (wt %)		Al-3 g (wt %)	
Alendronate sodium	0.30	(8.5)	0.30	(8.3)	0.30	(8.2)
Glycerin	1.00	(28.2)	1.00	(27.8)	1.00	(27.4)
NaOH	0		0.05	(1.4)	0.10	(2.7)
PIB adhesive	2.25	(63.4)	2.25	(62.5)	2.25	(61.6)

DETD . . . (13.4) 1.20 (13.3)

PIB adhesive (30% solid)	7.00	(78.7)	7.00	(78.0)	7.00	(77.4)
NaOH	0		0.04	(0.4)	0.07	(0.8)
DI water	0		0.04	(0.4)	0.07	(0.8)

DETD . . . Pax-2 Pax-3

	g (wt %)		g (wt %)		g (wt %)	
Paroxetine HCl	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
DI Water	0.30	(5.1)	0.35	(5.8)	0.40	(6.6)
THF	0.20	(3.4)	0.20	(3.3)	0.20	(3.3)
NaOH	0		0.05	(0.8)	0.10	(1.6)
Benzyl Alcohol	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
Glycerin	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
PIB adhesive (30% solid)	4.00	(67.8)	4.00	(66.7)	4.00	(65.6)
n-Heptane	0.50	(8.5)	0.50.	.	.	

DETD . . . 0.30 (14.3) 0.30 (14.0) 0.30 (13.6)

NaOH	0		0.05	(2.3)	0.10	(4.5)
Benzyl Alcohol	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
Glycerin	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
PIB adhesive	1.20	(57.1)	1.20	(55.8)	1.20	(54.5)

DETD . . . measured as described in the Methods section. Three diffusion cells were used for each formulation. The receiver solution, 5% N-methylpyrrolidone/95% water, was completely withdrawn and replaced with fresh receiver solution at each time point. The samples taken were analyzed by an. . .

DETD . . . Weight

	Gala-1 g (wt %)		Gala-2 g (wt %)		Gala-3 g (wt %)	
Galanthamine HBr	0.40	(4.7)	0.40	(4.6)	0.40	(4.6)
DI Water	0.30	(3.5)	0.34	(3.9)	0.38	(4.3)
NaOH	0		0.04	(0.5)	0.08	(0.9)
Glycerin	1.00	(11.6)	1.00	(11.5)	1.00	(11.4)
Benzyl Alcohol	0.40	(4.7)	0.40	(4.6)	0.40	(4.6)
PIB adhesive (30%. . .	6.00	(69.8)	6.00	(69.1)	6.00	(68.5)

DETD . . . g (wt %) g (wt %) g (wt %)

Galanthamine HBr	0.40	(11.1)	0.40	(11.0)	0.40	(10.9)
NaOH	0		0.04	(1.1)	0.08	(2.2)
Glycerin	1.00	(27.8)	1.00	(27.5)	1.00	(27.2)
Benzyl Alcohol	0.40	(11.1)	0.40	(11.0)	0.40	(10.9)
PIB adhesive	1.80	(50.0)	1.80	(49.5)	1.80	(48.9)

DETD . . . Weight

Hymo-1	Hymo-2	Hymo-3

	g (wt %)	g (wt %)	g (wt %)
Hydromorphone HCl	0.20 (2.8)	0.20 (2.7)	0.20 (2.7)
DI Water	0.30 (4.1)	0.38 (5.1)	0.43 (5.7)
NaOH	0	0.08 (1.0)	0.13 (1.7)
Glycerin	1.25 (17.2)	1.25 (16.9)	1.25 (16.7)
PIB adhesive (30% solid)	5.00 (69.0)	5.00 (67.6)	4.00 (66.7)
n-Heptane	0.50 (6.9)	0.50 (6.8)	0.50 (6.7)

DETD . . . g (wt %) g (wt %) g (wt %)

Hydromorphone HCl	0.20 (6.8)	0.20 (6.6)	0.20 (6.5)
NaOH	0	0.08 (2.5)	0.13 (4.1)
Glycerin	1.25 (42.4)	1.25 (41.3)	1.25 (41.7)
PIB adhesive	1.50 (50.8)	1.50 (49.6)	1.50 (48.8)

DETD . . . g (wt %) g (wt %)

Lidocaine	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
PG	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
Water	0	0.07 (1.2)	0.11 (1.8)
PIB adhesive (30% solid)	4.00 (72.7)	4.00 (70.9)	4.00 (70.1)
NaOH	0	0.07 (1.2)	0.11. . .

DETD . . . %) g (wt %)

Enalapril Maleate	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
PG	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
DI Water	0.20 (3.5)	0.33 (5.5)	0.45 (7.3)
NaOH	0	0.13 (2.1)	0.25 (4.0)
PIB adhesive	4.00 (70.2)	4.00 (67.2)	4.00 (64.5)

. . .

L11 ANSWER 4 OF 10 USPATFULL on STN

ACCESSION NUMBER: 2004:280961 USPATFULL

TITLE: Transdermal and topical administration of drugs using basic permeation enhancers

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040220262	A1	20041104
APPLICATION INFO.:	US 2004-860887	A1	20040603 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-177436, filed on 20 Jun 2002, PENDING Continuation-in-part of Ser. No. US 2001-972008, filed on 4 Oct 2001, GRANTED, Pat. No. US 6582724 Continuation-in-part of Ser. No. US 2000-738410, filed on 14 Dec 2000, GRANTED, Pat. No. US 6586000 Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-738395, filed on 14 Dec 2000, GRANTED, Pat. No. US 6719997 Continuation-in-part of Ser. No. US 2000-607892, filed on 30 Jun 2000, ABANDONED

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & EBERLE LLP, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 4380
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0017] The term "aqueous" refers to a composition, formulation or drug delivery system that contains water or that becomes water-containing following application to the skin or mucosal tissue.

DETD [0018] The term "base" is used in its traditional sense, i.e., a substance that dissolves in water to produce hydroxide ions. The water is typically an aqueous fluid, and may be natural moisture at the skin surface, or the patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . ointments, etc., may experience a net loss of moisture after being applied to the body surface, i.e., the amount of water lost is greater than the amount of water received from the body surface. In that case, the pH of the formulation may be different than its pH when. . .

DETD . . . N)

Sodium hydroxide.sup.1,2,3	14 (5%), 13 (0.5%), 12 (0.05%)
Potassium hydroxide.sup.1,2,3	13.5 (0.1 M)
Calcium hydroxide.sup.1,3	12.4 (saturated solution in water)
Magnesium hydroxide.sup.1,3	9.5 to 10.5 slurry
Magnesium oxide.sup.1,2,3	10.3 (saturated aqueous solution)
Calcium oxide.sup.3	Soluble in water, Form Ca(OH).sub.2
Sodium acetate.sup.1,3	.about.8.9 (0.1 N)
Sodium acetate, trihydrate.sup.1,2	8.9 (0.1 N)
Sodium acetate, anhydrous.sup.1,2	.about.8.9 (0.1 N)

Sodium. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine, . . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water is preferably present in order for the hydroxide ions to be provided by the base, and thus enhance the flux. . . the active agent through the patient's body surface. Thus, such a formulation or drug reservoir may be aqueous,

i.e., contain water, or may be nonaqueous and used in combination with an occlusive backing layer so that moisture evaporating from the body. . .

DETD . . . Pharmacy, 20.sup.th edition (Lippincott Williams & Wilkins, 2000), ointment foundations may be grouped in four classes: oleaginous, emulsifiable, emulsion, and water-soluble. Oleaginous ointment foundations include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment foundations, also known as absorbent ointment foundations, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment foundations are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment foundations are prepared from polyethylene glycols of varying molecular weight.

DETD [0240] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream foundations are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . acceptable chemicals to buffer, stabilize or preserve the solute. Commonly used examples of solvents used in preparing solutions are ethanol, water, propylene glycol or any other pharmaceutically acceptable vehicle.

DETD . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl

alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . of the patches was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added. The liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

DETD . . . g (wt %) g (wt %) g (wt %)

Estradiol	0.0313	(0.5)	0.0322	(0.5)	0.0308	(0.5)
NaOH	0		0.0155	(0.3)	0.025	(0.4)
DI water	0		0.4155	(6.9)	0.425	(7.0)
PIB adhesive (30% solid)	4	(66.3)	4	(66.0)	4	(65.8)
Methylal	1.8	(29.8)	1.4	(23.1)	1.4	(23.0)
Ethanol	0.2. . .					

DETD . . . in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with a 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the concentration of estradiol in the. . .

DETD . . . (wt %) g (wt %)

Ketoprofen	1.2	(16.7)	1.2	(15.8)	1.2	(15.7)	1.2 (15.7)	
NaOH	0		0.19	(2.5)	0.215	(2.8)	0.225 (2.9)	
DI water	0		0.19	(2.5)	0.215	(2.8)	0.225 (2.9)	
PIB adhesive (30% solid)	4	(55.6)	4	(52.8)	4	(52.4)	4 (52.3)	
Methylal	2	(27.8)	2. . .					

DETD . . . (wt %) g (wt %)

PPA-HCl	0.75	(8.5)	0.75	(8.2)	0.75	(8.1)	0.75 (8.1)	
NaOH	0		0.165	(1.8)	0.195	(2.1)	0.23 (2.5)	
DI water	1.1	(12.4)	1.265	(13.8)	1.295	(14.0)	1.33 (14.3)	
PG	0.5	(5.6)	0.5	(5.4)	0.5	(5.4)	0.5 (5.4)	
Methylal	1	(11.3)	1	(10.9). . .				

DETD . . . as described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with DI water. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . .

DETD . . . % g (wt %)

Ketoprofen 2.4 (14.0) 2.4 (14.0) 2.4 (13.9) 2.4 (13.8)
NaOH 0.6 (3.5) 0.65 (3.8) 0.69 (4.0) 0.73 (4.2)
DI water 0.6 (3.5) 0.65 (3.8) 0.69 (4.0) 0.73 (4.2)
Tetraglycol 0.5 (2.9) 0.5 (2.9) 0.5 (2.9) 0.5 (2.9)
Isopropyl- 0.4 (2.3) 0.4 (2.3). . .
DETD . . . (32.3) 0.6 (31.6) 0.6 (31.1)
NaOH 0 0.115 (6.2) 0.135 (7.1) 0.15 (7.8)
Ethanol 0.4 (24.5) 0.4 (21.5) 0.4 (21.1) 0.4 (20.7)
DI water 0.6 (36.8) 0.715 (38.4) 0.735 (38.7) 0.75 (38.9)
HPMCP 0.03 (1.8) 0.03 (1.6) 0.03 (1.6) 0.03 (1.6)
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.7) 0.5 (5.7) 0.5 (5.6) 0.5 (5.5)
Na.sub.2CO.sub.3 0 0.29 (3.3) 0.44 (5.0) 0.74 (8.1)
DI water 1.0 (13.5) 2.0 (23.0) 2.0 (22.6) 2.0 (21.9)
Methyl alcohol 0.5 (6.7) 0.5 (5.7) 0.5 (5.6) 0.5 (5.5)
PG 0.2 (2.7) 0.2. . .
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.6) 0.5 (6.1) 0.5 (6.1) 0.5 (6.1)
K.sub.3PO.sub.4 0 0.57 (7.0) 0.6 (7.3) 0.66 (8.0)
DI water 1.0 (13.2) 1.0 (12.2) 1.0 (12.2) 1.0 (12.1)
PG 0.5 (6.6) 0.5 (6.1) 0.5 (6.1) 0.5 (6.1)
Methyl alcohol 0.5 (6.6) 0.5. . .
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.9) 0.5 (6.4) 0.5 (6.3) 0.5 (6.1)
K.sub.3PO.sub.4 0 0.57 (7.3) 0.73 (9.2) 1.05 (12.7)
DI water 1.0 (13.9) 1.0 (12.9) 1.0 (12.6) 1.0 (12.1)
Methyl alcohol 0.5 (6.9) 0.5 (6.4) 0.5 (6.3) 0.5 (6.1)
PG 0.2 (2.8) 0.2. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . 0.03 (0.5) 0.03 (0.4)
Methyl alcohol 0.5 (8.0) 0.5 (7.8) 0.5 (7.6) 0.5 (7.4)
K.sub.3PO.sub.4 0 0.1 (1.6) 0.3 (4.6) 0.48 (7.1)
DI water 0.5 (8.0) 0.5 (7.8) 0.5 (7.6)

0.5 (7.4)
PG 0.25 (4.0) 0.25 (3.9) 0.25 (3.8) 0.25
(3.7)
PIB adhesive 4 (63.7) 4. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . (wt %) g (wt %)

Estradiol 0.03 (0.5) 0.03 (0.4) 0.03 (0.4) 0.03
(0.4)
Na.sub.2CO.sub.3 0 0.11 (1.6) 0.3 (4.1) 0.45
(6.1)
DI water 0.5 (8.0) 1.2 (16.9) 1.2 (16.5)
1.2 (16.2)
Methyl alcohol 0.5 (8.0) 0.5 (7.1) 0.5 (6.9) 0.5
(6.7)
PIB adhesive 4 (63.7). . .
DETD . . . to 23.3%. This behavior may be because the amount of Na.sub.2CO.sub.3 that could be dissolved by the small amount of water on the top of the skin remained about the same for Est-12, Est-13 and Est-14.
DETD . . . (wt %) g (wt %)

Estradiol 0.03 (0.5) 0.03 (0.4) 0.03 (0.4) 0.03
(0.4)
MgO 0 0.11 (1.6) 0.3 (4.1) 0.45
(6.1)
DI water 0.5 (8.0) 1.2 (16.9) 1.2 (16.5)
1.2 (16.2)
Methyl 0.5 (8.0) 0.5 (7.1) 0.5 (6.9) 0.5
(6.7)
alcohol
PIB 4 (63.7) 4 (56.4). . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.9) 0.5 (6.0) 0.5 (5.9) 0.5
(5.7)
MgO 0 0.11 (1.3) 0.26 (3.1) 0.50
(5.7)
DI water 1.0 (13.9) 2.0 (24.0) 2.0 (23.6)
2.0 (22.9)
Methyl alcohol 0.5 (6.9) 0.5 (6.0) 0.5 (5.9) 0.5
(5.7)
PG 0.2 (2.8) 0.2. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.
DETD . . . Leu-3*
g (wt %) g (wt %) g (wt %)

Leu- 0.003 (0.4) 6.4 + 10.sup.-4 (0.18) 6.4 +
10.sup.-4 (0.16)
prolide
DI water 0.45 (64.0) 0.28 (80.9) 0.33 (80.3)
NaOH 0 0.0125 (3.6) 0.0275 (6.7)
PG 0.25 (35.6) 0.053 (15.3) 0.053 (13.0)

*Solutions Leu-2 and Leu-3 were prepared using 0.15 g of Leu-1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.

DETD [0369] The cells were filled with DI water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography) to. . .

DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .

DETD . . . was applied, the donor chamber was covered with parafilm.

TABLE 45

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0375] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . .

DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .

DETD . . . is applied, the donor chamber was covered with parafilm.

TABLE 47

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0379] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of oxytocin in the receiver. . .

DETD . . . 0.1 (1.5)

PIB adhesive (30% solid) 4 (61.5) 4 (60.9) 4 (60.6) 4 (59.7)

Heptane 1 (15.4) 1 (15.2) 1 (15.2) 1 (14.9)

DI water 0 0.035 (0.5) 0.05 (0.8) 0.1 (1.5)

DETD . . . described in the Methods section. Three diffusion cells were

used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in. . .

DETD . . . (13.7) 0.3 (13.50)									
sodium									
PG	0.6	(28.2)	0.6	(27.6)	0.6	(27.4)	0.6	(26.9)	
Ethyl alcohol (44.8)	1	(46.9)	1	(46.1)	1	(45.7)	1		
DI water (11.2)	0.2	(9.4)	0.22	(10.1)	0.23	(10.5)	0.25		
HPMC (1.3)	0.03	(1.4)	0.03	(1.4)	00.3	(1.4)	0.03		
NaOH	0		0.02	(0.9)	0.03.	. .			

DETD . . . from these gels was measured as described in Example 6. Three diffusion cells were used for each formulation. 10% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . .

DETD . . . (7.9) 0.5 (7.8) 0.5 (7.8)									
PG	0.5	(7.9)	0.5	(7.9)	0.5	(7.8)	0.5	(7.8)	
NaOH	0		0.02	(0.3)	0.04	(0.6)	0.075	(1.2)	
DI water 0.075 (1.2)	0		0.02	(0.3)	0.04	(0.6)			
PIB adhesive (30% solid)	4	(63.5)	4	(63.1)	4	(62.7)	4	(62.0)	
Heptane	1	(15.9)	1.	. .					

DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . .

DETD . . . 0.05 (0.8)								
PIB adhesive (30% solid)	4	(61.5)	4	(61.3)	4	(61.2)	4	(60.6)
Heptane	1	(15.4)	1	(15.3)	1	(15.3)	1	(15.2)
DI water 0.05 (0.8)	0		0.01	(0.2)	0.02	(0.3)		

DETD . . . described in the Methods section. Twelve diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . .

DETD . . . Solution	Weight					
	Al-1		Al-2		Al-3	
	g	(wt %)	g	(wt %)	g	(wt %)
Alendronate sodium	0.30	(3.2)	0.30	(3.2)	0.30	(3.2)
Glycerin	1.00	(10.8)	1.00	(10.6)	1.00	(10.5)
NaOH	0		0.05	(0.5)	0.10	(1.1)
PIB adhesive (30% solid)	7.5	(80.6)	7.5	(79.8)	7.5	(78.9)

Heptane	0.50	(5.4)	0.50	(5.3)	0.50	(5.3)
DI water	0		0.05	(0.5)	0.10	(1.1)
DETD . . .	Film Weight					
	Al-1		Al-2		Al-3	
	g (wt %)		g (wt %)		g (wt %)	
Alendronate sodium	0.30	(8.5)	0.30	(8.3)	0.30	(8.2)
Glycerin	1.00	(28.2)	1.00	(27.8)	1.00	(27.4)
NaOH	0		0.05	(1.4)	0.10	(2.7)
PIB adhesive	2.25	(63.4)	2.25	(62.5)	2.25	(61.6)
DETD . . .	(4.4)					
Tetraglycol	1.20	(13.5)	1.20	(13.4)	1.20	(13.3)
PIB adhesive (30% solid)	7.00	(78.7)	7.00	(78.0)	7.00	(77.4)
NaOH	0		0.04	(0.4)	0.07	(0.8)
DI water	0		0.04	(0.4)	0.07	(0.8)
DETD . . .	Weight					
	Pax-1		Pax-2		Pax-3	
	g (wt %)		g (wt %)		g (wt %)	
Paroxetine HCl	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
DI Water	0.30	(5.1)	0.35	(5.8)	0.40	(6.6)
THF	0.20	(3.4)	0.20	(3.3)	0.20	(3.3)
NaOH	0		0.05	(0.8)	0.10	(1.6)
Benzyl Alcohol	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
Glycerin	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
PIB adhesive (30% solid)	4.00	(67.8)	4.00	(66.7)	4.00	(65.6)
n-Heptane	0.50	(8.5)	0.50	(8.3)	0.50	(8.2)
DETD . . .	(wt %)					
Paroxetine HCl	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
NaOH	0		0.05	(2.3)	0.10	(4.5)
Benzyl Alcohol	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
Glycerin	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
PIB adhesive	1.20	(57.1)	1.20	(55.8)	1.20	(54.5)

DETD . . . measured as described in the Methods section. Three diffusion cells were used for each formulation. The receiver solution, 5% N-methylpyrrolidone/95% water, was completely withdrawn and replaced with fresh receiver solution at each time point. The samples taken were analyzed by an. . .

DETD . . . Weight

	Gala-1		Gala-2		Gala-3	
	g (wt %)		g (wt %)		g (wt %)	
Galanthamine HBr	0.40	(4.7)	0.40	(4.6)	0.40	(4.6)
DI Water	0.30	(3.5)	0.34	(3.9)	0.38	(4.3)
NaOH	0		0.04	(0.5)	0.08	(0.9)
Glycerin	1.00	(11.6)	1.00	(11.5)	1.00	(11.4)
Benzyl Alcohol	0.40	(4.7)	0.40	(4.6)	0.40	(4.6)
PIB adhesive (30%. . .	6.00	(69.8)	6.00	(69.1)	6.00	(68.5)
DETD . . .	g (wt %)		g (wt %)		g (wt %)	
Galanthamine HBr	0.40	(11.1)	0.40	(11.0)	0.40	(10.9)
NaOH	0		0.04	(1.1)	0.08	(2.2)
Glycerin	1.00	(27.8)	1.00	(27.5)	1.00	(27.2)
Benzyl Alcohol	0.40	(11.1)	0.40	(11.0)	0.40	(10.9)
PIB adhesive	1.80	(50.0)	1.80	(49.5)	1.80	(48.9)
DETD . . .	Weight					

	Hymo-1 g (wt %)	Hymo-2 g (wt %)	Hymo-3 g (wt %)
Hydromorphone HCl	0.20 (2.8)	0.20 (2.7)	0.20 (2.7)
DI Water	0.30 (4.1)	0.38 (5.1)	0.43 (5.7)
NaOH	0	0.08 (1.0)	0.13 (1.7)
Glycerin	1.25 (17.2)	1.25 (16.9)	1.25 (16.7)
PIB adhesive (30% solid)	5.00 (69.0)	5.00 (67.6)	4.00 (66.7)
n-Heptane	0.50 (6.9)	0.50 (6.8)	0.50 (6.7)
DETD . . . g (wt %)	g (wt %)	g (wt %)	
Hydromorphone HCl	0.20 (6.8)	0.20 (6.6)	0.20 (6.5)
NaOH	0	0.08 (2.5)	0.13 (4.1)
Glycerin	1.25 (42.4)	1.25 (41.3)	1.25 (41.7)
PIB adhesive	1.50 (50.8)	1.50 (49.6)	1.50 (48.8)
DETD . . . g (wt %)	g (wt %)		
Lidocaine	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
PG	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
Water	0	0.07 (1.2)	0.11 (1.8)
PIB adhesive (30% solid)	4.00 (72.7)	4.00 (70.9)	4.00 (70.1)
NaOH	0	0.07 (1.2)	0.11. . .
DETD . . . %)	g (wt %)	g (wt %)	
Enalapril Maleate	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
PG	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
DI Water	0.20 (3.5)	0.33 (5.5)	0.45 (7.3)
NaOH	0	0.13 (2.1)	0.25 (4.0)
PIB adhesive (30% solid)	4.00 (70.2)	4.00 (67.2)	4.00 (64.5)
n-Heptane	0.50. . .		

L11 ANSWER 5 OF 10 USPATFULL on STN

ACCESSION NUMBER:	2003:318293 USPATFULL
TITLE:	Hydroxide-releasing agents as skin permeation enhancers
INVENTOR(S):	Luo, Eric C., Plano, TX, UNITED STATES Jacobson, Eric C., San Diego, CA, UNITED STATES Hsu, Tsung-Min, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030224035	A1	20031204
APPLICATION INFO.:	US 2003-371352	A1	20030219 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-738410, filed on 14 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, ABANDONED		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	REED & EBERLE LLP, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025		
NUMBER OF CLAIMS:	58		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	14 Drawing Page(s)		
LINE COUNT:	3563		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . the hydroxide-releasing agent prior to transdermal drug

administration. Such a solution will generally be comprised of a protic solvent (e.g., water or alcohol) and have a pH in the range of about 8.0 to 13, preferably 8.0 to 11.5, more preferably. . .

SUMM . . . surface or may involve use of a drug delivery device. In either case, it is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus enhance the flux of the active agent through the patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD [0049] The term "aqueous" refers to a formulation or drug delivery system that contains water or that becomes water -containing following application to the skin or mucosal tissue.

DETD . . . fluid may be natural moisture at the skin surface, or a patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water must be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus enhance the flux of the active agent through the patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD . . . Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water -in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy. . .

DETD [0138] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water -in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or

glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . side facing the receiver solution. Three diffusion cells were used for each formulation. The cells were filled with l0% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the concentration of estradiol in the. . .

DETD . . . the patch was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added; the liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . Systems

	Est-P18	Est-P19	Est-P20
Estradiol	0.0313 g (0.5%)	0.0322 g (0.5%)	0.0308 g (0.5%)
NaOH	0	0.0155 g	0.025 g

(0.3%) (0.4%)
DI water 0 0.4155 g 0.425 g
(6.9%) (7.0%)
PIB* adhesive (30% solid) 4 g 4 g 4 g
(66.3%) (66.0%) (65.8%)
Methylal 1.8. . .
DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .
DETD . . . 1.2 g 1.2 g 1.2 g
(16.7%) (15.8%) (15.7%) (15.7%)
NaOH 0 0.19 g 0.215 g 0.225 g
(2.5%) (2.8%) (2.9%)
DI water 0 0.19 g 0.215 g 0.225 g
(2.5%) (2.8%) (2.9%)
PIB adhesive 4 g 4 g 4 g 4 g
(30% solid). . .
DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .
DETD [0181] The cells were filled with DI water. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . . 0.75 g 0.75 g

(8.5%) (8.2%) (8.1%) (8.1%)
NaOH 0 0.165 g 0.195 g 0.23 g
(1.8%) (2.1%) (2.5%)
DI water 1.1 g 1.265 g 1.295 g 1.33 g
(12.4%) (13.8%) (14.0%) (14.3%)
Propylene glycol 0.5 g 0.5 g 0.5 g. . .
DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was cut. . .
DETD . . . 2.4 g 2.4 g
(14.0%) (14.0%) (13.9%) (13.8%)
NaOH 0.6 g 0.65 g 0.69 g 0.73 g
(3.5%) (3.8%) (4.0%) (4.2%)
DI water 0.6 g 0.65 g 0.69 g 0.73 g
(3.5%) (3.8%) (4.0%) (4.2%)
PIB adhesive (30% 8 g 8 g 8 g. . .
DETD . . . g 0.135 g 0.15 g
(6.2%) (7.1%) (7.8%)
Ethanol 0.4 g 0.4 g 0.4 g 0.4 g
(24.5%) (21.5%) (21.1%) (20.7%)
DI Water 0.6 g 0.715 g 0.735 g 0.75 g
(36.8%) (38.4%) (38.7%) (38.9%)
HPMCP* 0.03 g 0.03 g 0.03 g 0.03 g
. . .
DETD . . . 0.5 g 0.5 g 0.5 g
(6.7%) (5.7%) (5.6%) (5.5%)
Na.sub.2CO.sub.3 0 0.29 g 0.44 g 0.74 g
(3.3%) (5.0%) (8.1%)
DI water 1.0 g 2.0 g 2.0 g 2.0 g

	(13.5%)	(23.0%)	(22.6%)	(21.9%)
Methyl alcohol. . .	0.5 g	0.5 g	0.5 g	0.5 g
DETD . . .	0.5 g (6.6%)	0.5 g (6.1%)	0.5 g (6.1%)	(6.1%)
K.sub.3PO.sub.4	0	0.57 g (7.0%)	0.6 g (7.3%)	0.66 g (8.0%)
DI water	1.0 g (13.2%)	1.0 g (12.2%)	1.0 g (12.2%)	1.0 g (12.1%)
Propylene glycol. . .	0.5 g	0.5 g	0.5 g	0.5 g
DETD . . .	(6.9%)	0.5 g (6.4%)	0.5 g (6.3%)	5 g (6.1%)
K.sub.3PO.sub.4	0	0.57 g (7.3%)	0.73 g (9.2%)	1.05 g (12.7%)
DI water	1.0 g (13.9%)	1.0 g (12.9%)	1.0 g (12.6%)	1.0 g (12.1%)
Methyl	0.5 g (6.9%)	0.5 g	0.5 g	0.5. . .
DETD	. . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the PPA-HCl patch measured using the procedures listed above. . .			
DETD . . .	0.5 g	0.5 g (7.6%)	0.5 g	
alcohol	(8.0%)	(7.8%)		(7.4%)
K.sub.3PO.sub.4	0	0.1 g (1.6%)	0.3 g (4.6%)	0.48 g (7.1%)
DI water	0.5 g (8.0%)	0.5 g (7.8%)	0.5 g (7.6%)	0.5 g (7.4%)
Propylene	0.25 g	0.25 g	0.25 g (3.8%)	0.25. . .
DETD	. . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the estradiol patch measured using the procedures listed above. . .			
DETD . . .	0.03 g (0.5%)	0.03 g (0.4%)	(0.4%)	(0.4%)
Na.sub.2CO.sub.3	0	0.11 g (1.6%)	0.3 g (4.1%)	0.45 g (6.1%)
DI water	0.5 g (8.0%)	1.2 g (16.9%)	1.2 g (16.5%)	1.2 g (16.2%)
Methyl	0.5 g	0.5 g	0.5 g	0.5. . .
DETD	. . . and 34). This behavior may be because the amount of Na.sub.2CO.sub.3 that could be dissolved by the small amount of water on the top of the skin remained about the same for Est-PC2, Est-PC3 and Est-PC4. The pH of the estradiol. . .			
DETD . . .	(0.5%)	0.03 g (0.4%)	0.03 g (0.4%)	0.03 g (0.4%)
MgO	0	0.11 g (1.6%)	0.3 g (4.1%)	0.45 g (6.1%)
DI water	0.5 g (8.0%)	1.2 g (16.9%)	1.2 g (16.5%)	1.2 g (16.2%)
Methyl alcohol. . .	0.5 g	0.5 g	0.5 g	0.5 g
DETD	. . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the estradiol patch measured using the procedures listed above. . .			
DETD . . .	0.5 g (6.9%)	0.5 g (6.0%)	0.5 g (5.9%)	0.5 g (5.7%)
MgO	0	0.11 g (1.3%)	0.26 g (3.1%)	0.50 g (5.7%)

DI water 1.0 g 2.0 g 2.0 g 2.0 g
(22.9%)
(13.9%) (24.0%) (23.6%)
Methyl 0.5 g 0.5 g 0.5 g 0.5 g. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced. The pH of the PPA-HCl patch measured using the procedures listed above. . .
DETD . . . cells were used for each test group for a total of 18 cells. The cells were filled with deionized (DI) water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography) to. . . Solutions

	Leu-S1	Leu-S2*	Leu-S3*
Leuprolide	0.003 g	6.4 + 10.sup.-4 g	6.4 g + 10.sup.-4 g
	(0.4%)	(0.18%)	(0.16%)
DI water	0.45 g	0.28 g	0.33 g
	(64.0%)	(80.9%)	(80.3%)
NaOH	0 g	0.0125 g	0.0275 g
	(0.0%)	(3.6%)	(6.7%)
Propylene. . .	(13.0%)		

*Solutions Leu-S2 and Leu-3 were prepared using 0.15 g of Leu-S1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.
DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . . 45. Once the oxytocin solution is applied, the donor chamber was covered with parafilm. The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . . for each time point, which were listed in Table 46.
TABLE 45

Formulation for the Oxytocin Solution

Oxytocin	0.005 g
DI water	0.6 g
Propylene Glycol	0.6 g

DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . . 47. Once the oxytocin solution is applied, the donor chamber was covered with parafilm. The cells were filled with DI water as a receiver solution. The DI water has been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of

oxytocin in the receiver. . . for each time point, which were listed in Table 48.

TABLE 47

Formulation for the Oxytocin Solution

Oxytocin	0.005 g
DI water	0.6 g
Propylene Glycol	0.6 g

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . side facing the receiver solution. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in. . .

DETD . . . of the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water /patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . 4 g 4 g

solid)	(61.5%)	(60.9%)	(60.6%)	(59.7%)
Heptane	1 g	1 g	1 g	1 g
	(15.4%)	(15.2%)	(15.2%)	(14.9%)
DI water	0	0.035 g	0.05 g	0.1 g
		(0.5%)	(0.8%)	(1.5%)

DETD . . . cell with the stratum corneum side facing the donor solution. Three diffusion cells were used for each formulation. 10% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . . glycol (28.2%) (27.6%) (27.4%) (26.9%)

Ethyl alcohol	1 g	1 g	1 g	1 g
	(46.9%)	(46.1%)	(45.7%)	(44.8%)
DI water	0.2 g	0.22 g	0.23 g	0.25 g
	(9.4%)	(10.1%)	(10.5%)	(11.2%)
HPMC	0.03 g	0.03 g	00.3 g	0.03. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . side facing the receiver solution. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . .

DETD . . . the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added,

the liner was removed from patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water /patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . 0.5 g 0.5 g 0.5 g

glycol	(7.9%)	(7.9%)	(7.8%)	(7.8%)
NaOH	0	0.02 g	0.04 g	0.075 g
		(0.3%)	(0.6%)	(1.2%)
DI water	0	0.02 g	0.04 g	0.075 g
		(0.3%)	(0.6%)	(1.2%)
PIB adhesive (30% solid). . .	4 g	4 g	4 g	4 g

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0288] The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of oxybutynin HCl in. . . Solution Weight) for Three Oxybutynin HCl Transdermal Systems

	Oxy-P1	Oxy-P2	Oxy-P3
Oxybutynin HCl	0.5 g (6.5%)	0.5 g (6.3%)	0.5 g (6.2%)
DI water	0.65 g (8.4%)	0.75 g (9.5%)	0.85 g (10.5%)
NaOH	0.15 g (1.9%)	0.25 g (3.2%)	0.35 g (4.3%)
Propylene glycol	0.3. . .		

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0294] The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . . interface were listed in Table 65. For all other cells, the receiving fluid was completely withdrawn and replaced with fresh ethanol/water solution. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in the receiver solution. The. . .

DETD . . . the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . . g 4 g

(30% solid)	(61.5%)	(61.3%)	(61.2%)	(60.6%)
Heptane	1 g	1 g	1 g	1 g
	(15.4%)	(15.3%)	(15.3%)	(15.2%)
DI water	0	0.01 g	0.02 g	0.05 g
		(0.2%)	(0.3%)	(0.8%)

L11 ANSWER 6 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2003:231672 USPATFULL
TITLE: Dual enhancer composition for topical and transdermal drug delivery
INVENTOR(S): Hsu, Tsung-Min, San Diego, CA, UNITED STATES

Jacobson, Eric C., San Diego, CA, UNITED STATES
LoBello, Rose C., San Diego, CA, UNITED STATES
Luo, Eric C., Plano, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030161870	A1	20030828
	US 6835392	B2	20041228
APPLICATION INFO.:	US 2003-389143	A1	20030313 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-972008, filed on 4 Oct 2001, GRANTED, Pat. No. US 6582724 Continuation-in-part of Ser. No. US 2000-738410, filed on 14 Dec 2000, GRANTED, Pat. No. US 6586000 Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & EBERLE LLP, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 48
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1922
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . to the body surface or may involve use of a drug delivery device. It is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus assist in enhancing the flux of the active agent through a patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD . . . fluid may be natural moisture at the skin surface, or a patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . increases with the value of the Hildebrand solubility parameter. For example, the skin has a σ value of 10, while water has a σ value of 23.4. This in turn means enhancers with solubility parameters of <10 will intervene with the. . .

DETD . . . components of the composition. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin; . . .

DETD . . . like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. It is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus assist in enhancing the flux of the active agent through a patient's body surface. Thus, the formulation may be aqueous, i.e., contain water, or may be nonaqueous and optionally used in combination with an occlusive overlayer so that moisture evaporating from the body. . .

DETD . . . Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also

known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy. . .

DETD [0076] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridamine, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated on a release liner and dried in an oven

at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . .	0.25 g	0.25 g		
THF	1.25 g	1.25 g	1.25 g	1.25 g
Benzyl alcohol	0.7 g	0.7 g	0.7 g	0.7 g
Glycerin	0.7 g	0.7 g	0.7 g	0.7 g
Oleic acid	0	0.2 g	0	0.2 g
Protalan	0.15 g	0.15 g	0.15. . . g	0.3 g
0.3 g	0.3 g			
Urea	0.2 g	0.2 g	0.2 g	0.2 g
NaGH	0	0.09 g	0.09 g	0
Water	0	0.09 g	0.09 g	0
Testosterone	0.5 g	0.5 g	0.5 g	0.5 g

L11 ANSWER 7 OF 10 USPATFULL on STN

ACCESSION NUMBER: 2003:180349 USPATFULL

TITLE: Transdermal and topical administration of drugs using basic permeation enhancers

INVENTOR(S): Hsu, Tsung-Min, San Diego, CA, UNITED STATES
Gricenko, Nicole T., San Diego, CA, UNITED STATES
Hickey, Alan T.J., San Diego, CA, UNITED STATES
Jacobson, Eric C., San Diego, CA, UNITED STATES
LoBello, Rose C., San Diego, CA, UNITED STATES
Obara, Jane, San Diego, CA, UNITED STATES
Luo, Eric C., Plano, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030124176	A1	20030703
APPLICATION INFO.:	US 2002-176952	A1	20020621 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-972008, filed on 4 Oct 2001, PENDING Continuation-in-part of Ser. No. US 2000-738410, filed on 14 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, PENDING Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-738395, filed on 14 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-607892, filed on 30 Jun 2000, ABANDONED

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025

NUMBER OF CLAIMS: 72

EXEMPLARY CLAIM: 1

LINE COUNT: 4440

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0017] The term "aqueous" refers to a composition, formulation or drug delivery system that contains water or that becomes water-containing following application to the skin or mucosal tissue.

SUMM [0018] The term "base" is used in its traditional sense, i.e., a substance that dissolves in water to produce hydroxide ions. The water is typically an aqueous fluid, and may be natural moisture at the skin surface, or the patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

SUMM . . . ointments, etc., may experience a net loss of moisture after being applied to the body surface, i.e., the amount of water lost is greater than the amount of water received from the body surface. In that case, the pH of the formulation may be different than its pH when. . .

SUMM . . . N), 10.27 (0.001 N)

Sodium hydroxide.sup.1,2,3	14 (5%), 13 (0.5%), 12 (0.05%)
Potassium hydroxide.sup.1,2,3	13.5 (0.1 M)
Calcium hydroxide.sup.1,3 water)	12.4 (saturated solution in
Magnesium hydroxide.sup.1,3	9.5 to 10.5 slurry
Magnesium oxide.sup.1,2,3	10.3 (saturated aqueous solution)
Calcium oxide.sup.3 Ca(OH).sub.2	Soluble in water, Form
Sodium acetate.sup.1,3	.about.8.9 (0.1 N)
Sodium acetate, trihydrate.sup.1,2	8.9 (0.1 N)
Sodium acetate, anhydrous.sup.1,2	.about.8.9 (0.1 N)
Sodium borate decahydrate.sup.1,2	.about.8.8-9.4, 9.15. . .

SUMM . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

SUMM . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

SUMM . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water is preferably present in order for the hydroxide ions to be provided by the base, and thus enhance the flux. . . the active agent through the patient's body surface. Thus, such a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive backing layer so that moisture evaporating from the body. . . Pharmacy, 20.sup.th edition (Lippincott Williams & Wilkins, 2000), ointment foundations may be grouped in four classes: oleaginous, emulsifiable, emulsion, and water-soluble. Oleaginous ointment foundations include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment foundations, also known as absorbent ointment foundations, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment foundations are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment foundations are prepared from polyethylene glycols of varying molecular weight.

SUMM [0235] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream foundations are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

SUMM . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by

trituration, mechanical mixing or stirring, or combinations thereof.

SUMM . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

SUMM . . . acceptable chemicals to buffer, stabilize or preserve the solute. Commonly used examples of solvents used in preparing solutions are ethanol, water, propylene glycol or any other pharmaceutically acceptable vehicle.

SUMM . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

SUMM . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

SUMM . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

SUMM . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate)(poly(HEMA)), or a copolymer or mixture thereof. Particularly. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . of the patches was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added. The liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

DETD . . . g (wt %) g (wt %) g (wt %)

Estradiol	0.0313 (0.5)	0.0322 (0.5)	0.0308 (0.5)
NaOH	0	0.0155 (0.3)	0.025 (0.4)
DI water	0	0.4155 (6.9)	0.425 (7.0)
PIB adhesive (30% solid)	4 (66.3)	4 (66.0)	4 (65.8)
Methylal	1.8 (29.8)	1.4 (23.1)	1.4 (23.0)

Ethanol. . .

DETD . . . in the Methods section. Three diffusion cells were used for

each formulation. The cells were filled with a 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the concentration of estradiol in the. . .

DETD . . . (wt %)		g (wt %)		
Ketoprofen	1.2 (16.7)	1.2 (15.8)	1.2 (15.7)	1.2 (15.7)
NaOH	0	0.19 (2.5)	0.215 (2.8)	0.225 (2.9)
DI water	0	0.19 (2.5)	0.215 (2.8)	0.225 (2.9)
PIB adhesive (30% solid)	4 (55.6)	4 (52.8)	4 (52.4)	4 (52.3)
Methylal	2 (27.8)	2. . .		
DETD . . . (wt %)		g (wt %)		
PPA-HCl	0.75 (8.5)	0.75 (8.2)	0.75 (8.1)	0.75 (8.1)
NaOH	0	0.165 (1.8)	0.195 (2.1)	0.23 (2.5)
DI water	1.1 (12.4)	1.265 (13.8)	1.295 (14.0)	1.33 (14.3)
PG	0.5 (5.6)	0.5 (5.4)	0.5 (5.4)	0.5 (5.4)
Methylal	1 (11.3)	1 (10.9). . .		

DETD . . . as described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with DI water . The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . .

DETD . . . %)		g (wt %)		
Ketoprofen		2.4 (14.0)	2.4 (14.0)	2.4 (13.9) 2.4 (13.8)
NaOH		0.6 (3.5)	0.65 (3.8)	0.69 (4.0) 0.73 (4.2)
DI water		0.6 (3.5)	0.65 (3.8)	0.69 (4.0) 0.73 (4.2)
Tetraglycol		0.5 (2.9)	0.5 (2.9)	0.5 (2.9) 0.5 (2.9)
Isopropylmyristate		0.4 (2.3)	0.4 (2.3). . .	
DETD . . . (32.3)		0.6 (31.6)	0.6 (31.1)	
NaOH	0	0.115 (6.2)	0.135 (7.1)	0.15 (7.8)
Ethanol	0.4 (24.5)	0.4 (21.5)	0.4 (21.1)	0.4 (20.7)
DI water	0.6 (36.8)	0.715 (38.4)	0.735 (38.7)	0.75 (38.9)
HPMCP	0.03 (1.8)	0.03 (1.6)	0.03 (1.6)	0.03 (1.6)
DETD . . . (wt %)		g (wt %)		
PPA-HCl	0.5 (6.7)	0.5 (5.7)	0.5 (5.6)	0.5 (5.5)
Na.sub.2CO.sub.3	0	0.29 (3.3)	0.44 (5.0)	0.74 (8.1)
DI water	1.0 (13.5)	2.0 (23.0)	2.0 (22.6)	2.0 (21.9)
Methyl alcohol	0.5 (6.7)	0.5 (5.7)	0.5 (5.6)	0.5 (5.5)
PG	0.2 (2.7)	0.2. . .		
DETD . . . (wt %)		g (wt %)		
PPA-HCl	0.5 (6.6)	0.5 (6.1)	0.5 (6.1)	0.5 (6.1)
K.sub.3PO.sub.4	0	0.57 (7.0)	0.6 (7.3)	0.66 (8.0)
DI water	1.0 (13.2)	1.0 (12.2)	1.0 (12.2)	1.0 (12.1)
PG	0.5 (6.6)	0.5 (6.1)	0.5 (6.1)	0.5 (6.1)
Methyl alcohol	0.5 (6.6)	0.5. . .		
DETD . . . (wt %)		g (wt %)		
PPA-HCl	0.5 (6.9)	0.5 (6.4)	0.5 (6.3)	0.5 (6.1)
K.sub.3PO.sub.4	0	0.57 (7.3)	0.73 (9.2)	1.05 (12.7)
DI water	1.0 (13.9)	1.0 (12.9)	1.0 (12.6)	1.0 (12.1)
Methyl alcohol	0.5 (6.9)	0.5 (6.4)	0.5 (6.3)	0.5 (6.1)
PG	0.2 (2.8)	0.2. . .		

DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of

water on the top of the skin was reduced.

DETD . . .	0.03 (0.5)	0.03 (0.4)		
Methyl alcohol	0.5 (8.0)	0.5 (7.8)	0.5 (7.6)	0.5 (7.4)
K.sub.3PO.sub.4	0	0.1 (1.6)	0.3 (4.6)	0.48 (7.1)
DI water	0.5 (8.0)	0.5 (7.8)	0.5 (7.6)	0.5 (7.4)
PG	0.25 (4.0)	0.25 (3.9)	0.25 (3.8)	0.25 (3.7)
PIB adhesive	4 (63.7)	4. . .		

DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD . . . (wt %) g (wt %)

Estradiol	0.03 (0.5)	0.03 (0.4)	0.03 (0.4)	0.03 (0.4)
Na.sub.2CO.sub.3	0	0.11 (1.6)	0.3 (4.1)	0.45 (6.1)
DI water	0.5 (8.0)	1.2 (16.9)	1.2 (16.5)	1.2 (16.2)
Methyl alcohol	0.5 (8.0)	0.5 (7.1)	0.5 (6.9)	0.5 (6.7)
PIB adhesive	4 (63.7). . .			

DETD . . . to 23.3%. This behavior may be because the amount of Na.sub.2CO.sub.3 that could be dissolved by the small amount of water on the top of the skin remained about the same for Est-12, Est-13 and Est-14.

DETD . . . (wt %) g (wt %)

Estradiol	0.03 (0.5)	0.03 (0.4)	0.03 (0.4)	0.03 (0.4)
MgO	0	0.11 (1.6)	0.3 (4.1)	0.45 (6.1)
DI water	0.5 (8.0)	1.2 (16.9)	1.2 (16.5)	1.2 (16.2)
Methyl alcohol	0.5 (8.0)	0.5 (7.1)	0.5 (6.9)	0.5 (6.7)
PIB adhesive	4 (63.7). . .			

DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD . . . (wt %) g (wt %)

PPA-HCl	0.5 (6.9)	0.5 (6.0)	0.5 (5.9)	0.5 (5.7)
MgO	0	0.11 (1.3)	0.26 (3.1)	0.50 (5.7)
DI water (22.9)	1.0 (13.9)	2.0 (24.0)	2.0 (23.6)	2.0
Methyl alcohol	0.5 (6.9)	0.5 (6.0)	0.5 (5.9)	0.5 (5.7)
PG	0.2 (2.8)	0.2. . .		

DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD . . . Weight

	Leu-1 g (wt %)	Leu-2* g (wt %)	Leu-3*
Leuprolide	0.003 (0.4)	6.4 + 10.sup.-4 (0.18)	6.4 + 10.sup.-4 (0.16)
DI water	0.45 (64.0)	0.28 (80.9)	0.33 (80.3)
NaOH	0	0.0125 (3.6)	0.0275 (6.7)
PG	0.25 (35.6)	0.053 (15.3)	0.053 (13.0)

*Solutions Leu-2 and Leu-3 were prepared using 0.15 g of Leu-1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.

DETD [0358] The cells were filled with DI water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography)

to. . .
DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .
DETD . . . was applied, the donor chamber was covered with parafilm.
TABLE 45

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0364] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . .
DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .
DETD . . . is applied, the donor chamber was covered with parafilm.
TABLE 47

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0368] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of oxytocin in the receiver. . .
DETD . . . 0.1 (1.5)

PIB adhesive (30% solid)	4 (61.5)	4 (60.9)	4 (60.6)	4 (59.7)
Heptane	1 (15.4)	1 (15.2)	1 (15.2)	1 (14.9)
DI water	0	0.035 (0.5)	0.05 (0.8)	0.1 (1.5)

DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in. . .
DETD . . . (13.7) 0.3 (13.50)

sodium				
PG	0.6 (28.2)	0.6 (27.6)	0.6 (27.4)	0.6 (26.9)
Ethyl alcohol	1 (46.9)	1 (46.1)	1 (45.7)	1 (44.8)
DI water	0.2 (9.4)	0.22 (10.1)	0.23 (10.5)	0.25 (11.2)
HPMC	0.03 (1.4)	0.03 (1.4)	00.3 (1.4)	0.03 (1.3)
NaOH	0	0.02 (0.9)	0.03. . .	

DETD . . . from these gels was measured as described in Example 6. Three diffusion cells were used for each formulation. 10% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . .

DETD . . . (7.9)	0.5 (7.8)	0.5 (7.8)		
PG	0.5 (7.9)	0.5 (7.9)	0.5 (7.8)	0.5 (7.8)
NaOH	0	0.02 (0.3)	0.04 (0.6)	0.075 (1.2)
DI water	0	0.02 (0.3)	0.04 (0.6)	0.075 (1.2)
PIB adhesive (30% solid)	4 (63.5)	4 (63.1)	4 (62.7)	4 (62.0)
Heptane	1 (15.9)	1. . .		

DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . .

DETD . . . 0.05 (0.8)				
PIB adhesive (30% solid)	4 (61.5)	4 (61.3)	4 (61.2)	4 (60.6)
Heptane	1 (15.4)	1 (15.3)	1 (15.3)	1 (15.2)
DI water	0	0.01 (0.2)	0.02 (0.3)	0.05 (0.8)

DETD . . . described in the Methods section. Twelve diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . .

DETD . . . Solution Weight

	A1-1 g (wt %)	A1-2 g (wt %)	A1-3 g (wt %)
Alendronate sodium	0.30 (3.2)	0.30 (3.2)	0.30 (3.2)
Glycerin	1.00 (10.8)	1.00 (10.6)	1.00 (10.5)
NaOH	0	0.05 (0.5)	0.10 (1.1)
PIB adhesive (30% solid)	7.5 (80.6)	7.5 (79.8)	7.5 (78.9)
Heptane	0.50 (5.4)	0.50 (5.3)	0.50 (5.3)
DI water	0	0.05 (0.5)	0.10 (1.1)

DETD . . . Film Weight

	A1-1 g (wt %)	A1-2 g (wt %)	A1-3 g (wt %)
Alendronate sodium	0.30 (8.5)	0.30 (8.3)	0.30 (8.2)
Glycerin	1.00 (28.2)	1.00 (27.8)	1.00 (27.4)
NaOH	0	0.05 (1.4)	0.10 (2.7)
PIB adhesive	2.25 (63.4)	2.25 (62.5)	2.25 (61.6)

DETD . . . (13.4)	1.20 (13.3)		
PIB adhesive (30% solid)	7.00 (78.7)	7.00 (78.0)	7.00 (77.4)
NaOH	0	0.04 (0.4)	0.07 (0.8)
DI water	0	0.04 (0.4)	0.07 (0.8)

DETD . . . Pax-2 Pax-3

	g (wt %)	g (wt %)	g (wt %)
Paroxetine HCl	0.30 (5.1)	0.30 (5.0)	0.30 (4.9)
DI Water	0.30(5.1)	0.35 (5.8)	0.40 (6.6)
THF	0.20 (3.4)	0.20 (3.3)	0.20 (3.3)
NaGH	0	0.05 (0.8)	0.10 (1.6)

Benzyl Alcohol	0.30 (5.1)	0.30 (5.0)	0.30 (4.9)
Glycerin	0.30 (5.1)	0.30 (5.0)	0.30 (4.9)
PIB adhesive (30% solid)	4.00 (67.8)	4.00 (66.7)	4.00 (65.6)
n-Heptane	0.50 (8.5)	0.50. . .	

DETD . . . 0.30 (14.3) 0.30 (14.0) 0.30 (13.6)

NaOH	0	0.05 (2.3)	0.10 (4.5)
Benzyl Alcohol	0.30 (14.3)	0.30 (14.0)	0.30 (13.6)
Glycerin	0.30 (14.3)	0.30 (14.0)	0.30 (13.6)
PIB adhesive	1.20 (57.1)	1.20 (55.8)	1.20 (54.5)

DETD . . . measured as described in the Methods section. Three diffusion cells were used for each formulation. The receiver solution, 5% N-methylpyrrolidone/95% water, was completely withdrawn and replaced with fresh receiver solution at each time point. The samples taken were analyzed by an. . .

DETD . . . Solution

Weight

	Gala-1 g (wt %)	Gala-2 g (wt %)	Gala-3 g (wt %)
Galanthamine HBr	0.40 (4.7)	0.40 (4.6)	0.40 (4.6)
DI Water	0.30 (3.5)	0.34 (3.9)	0.38 (4.3)
NaOH	0	0.04 (0.5)	0.08 (0.9)
Glycerin	1.00 (11.6)	1.00 (11.5)	1.00 (11.4)
Benzyl Alcohol	0.40 (4.7)	0.40 (4.6)	0.40 (4.6)
PIB adhesive (30%. . .	6.00 (69.8)	6.00 (69.1)	6.00 (68.5)

DETD . . . g (wt %) g (wt %) g (wt %)

Galanthamine HBr	0.40 (11.1)	0.40 (11.0)	0.40 (10.9)
NaOH	0	0.04 (1.1)	0.08 (2.2)
Glycerin	1.00 (27.8)	1.00 (27.5)	1.00 (27.2)
Benzyl Alcohol	0.40 (11.1)	0.40 (11.0)	0.40 (10.9)
PIB adhesive	1.80 (50.0)	1.80 (49.5)	1.80 (48.9)

DETD . . . Solution

Weight

	Hymo-1 g (wt %)	Hymo-2 g (wt %)	Hymo-3 g (wt %)
Hydromorphone HCl	0.20 (2.8)	0.20 (2.7)	0.20 (2.7)
DI Water	0.30 (4.1)	0.38 (5.1)	0.43 (5.7)
NaOH	0	0.08 (1.0)	0.13 (1.7)
Glycerin	1.25 (17.2)	1.25 (16.9)	1.25 (16.7)
PIB adhesive (30% solid)	5.00 (69.0)	5.00 (67.6)	4.00 (66.7)
n-Heptane	0.50 (6.9)	0.50 (6.8)	0.50 (6.7)

DETD . . . g (wt %) g (wt %) g (wt %)

Hydromorphone HCl	0.20 (6.8)	0.20 (6.6)	0.20 (6.5)
NaOH	0	0.08 (2.5)	0.13 (4.1)
Glycerin	1.25 (42.4)	1.25 (41.3)	1.25 (41.7)
PIB adhesive	1.50 (50.8)	1.50 (49.6)	1.50 (48.8)

DETD . . . g (wt %) g (wt %)

Lidocaine	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
PG	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
Water	0	0.07(1.2)	0.11 (1.8)
PIB adhesive (30% solid)	4.00 (72.7)	4.00 (70.9)	4.00 (70.1)
NaOH	0	0.07(1.2)	0.11 (1.8)

n-Heptane. . .			
DETD . . . %)	g (wt %)	g (wt %)	
Enalapril Maleate	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
PG	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
DI Water	0.20 (3.5)	0.33 (5.5)	0.45 (7.3)
NaOH	0	0.13 (2.1)	0.25 (4.0)
PIB adhesive (30% solid)	4.00 (70.2)	4.00 (67.2)	4.00 (64.5)
n-Heptane	0.50. . .		

L11 ANSWER 8 OF 10 USPATFULL on STN

ACCESSION NUMBER: 2003:152375 USPATFULL
TITLE: Transdermal and topical administration of drugs using basic permeation enhancers
INVENTOR(S): Hsu, Tsung-Min, San Diego, CA, UNITED STATES
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030104041	A1	20030605
APPLICATION INFO.:	US 2002-177436	A1	20020620 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-972008, filed on 4 Oct 2001, PENDING Continuation-in-part of Ser. No. US 2000-738410, filed on 14 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, PENDING Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, PENDING Continuation-in-part of Ser. No. US 2000-738395, filed on 14 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-607892, filed on 30 Jun 2000, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 72
EXEMPLARY CLAIM: 1
LINE COUNT: 4474
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0018] The term "aqueous" refers to a composition, formulation or drug delivery system that contains water or that becomes water-containing following application to the skin or mucosal tissue.

SUMM [0019] The term "base" is used in its traditional sense, i.e., a substance that dissolves in water to produce hydroxide ions. The water is typically an aqueous fluid, and may be natural moisture at the skin surface, or the patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

SUMM . . . ointments, etc., may experience a net loss of moisture after being applied to the body surface, i.e., the amount of water lost is greater than the amount of water received from the body surface. In that case, the pH of the formulation may be different than its pH when. . .

SUMM . . . 2, 3 14 (5%), 13 (0.5%), 12 (0.05%)
Potassium hydroxide.sup.1, 2, 3 13.5 (0.1 M)
Calcium hydroxide.sup.1, 3 12.4 (saturated solution in water)
Magnesium hydroxide.sup.1, 3 9.5 to 10.5 slurry
Magnesium oxide.sup.1, 2, 3 10.3 (saturated aqueous solution)
Calcium oxide.sup.3 Soluble in water, Form Ca(OH).sub.2
Sodium acetate.sup.1, 3 .about.8.9 (0.1 N)
Sodium acetate, trihydrate.sup.1, 2 8.9 (0.1 N)
Sodium acetate, anhydrous.sup.1, 2 .about.8.9 (0.1 N)
Sodium borate. . .

SUMM . . . dicyclomine, diethylpropriom, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

SUMM . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

SUMM . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water is preferably present in order for the hydroxide ions to be provided by the base, and thus enhance the flux. . . the active agent through the patient's body surface. Thus, such a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive backing layer so that moisture evaporating from the body. . .

SUMM . . . Pharmacy, 20.sup.th edition (Lippincott Williams & Wilkins, 2000), ointment foundations may be grouped in four classes: oleaginous, emulsifiable, emulsion, and water-soluble. Oleaginous ointment foundations include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment foundations, also known as absorbent ointment foundations, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment foundations are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment foundations are prepared from polyethylene glycols of varying molecular weight.

SUMM [0241] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream foundations are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

SUMM . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof.

SUMM . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily

emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

SUMM . . . acceptable chemicals to buffer, stabilize or preserve the solute. Commonly used examples of solvents used in preparing solutions are ethanol, water, propylene glycol or any other pharmaceutically acceptable vehicle.

SUMM . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

SUMM . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

SUMM . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

SUMM . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . of the patches was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added. The liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

DETD . . . (wt %) g (wt %) g (wt %)

Estradiol	0.0313 (0.5)	0.0322 (0.5)	0.0308 (0.5)
NaOH	0	0.0155 (0.3)	0.025 (0.4)
DI water	0	0.4155 (6.9)	0.425 (7.0)
PIB adhesive (30% solid)	.sup. 4 (66.3).sup.	4 (66.0)	4 (65.8)
Methylal Ethanol. . .	1.8 (29.8)	1.4 (23.1)	1.4 (23.0)

DETD . . . in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with a 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the

concentration of estradiol in the. . .
DETD . . . g (wt %)

Ketoprofen	1.2 (16.7)	.sup.	1.2 (15.8)	1.2 (15.7)	1.2 (15.7)
NaOH	0		0.19 (2.5)	0.215 (2.8)	0.225 (2.9)
DI water	0		0.19 (2.5)	0.215 (2.8)	0.225 (2.9)
PIB adhesive (30% solid)	4 (55.6)		4 (52.8)	4 (52.4)	4 (52.3)
Methylal	2 (27.8). . .				

DETD . . . g (wt %)

PPA-HCl	0.75 (8.5)	0.75 (8.2)	0.75 (8.1)	0.75 (8.1)
NaOH	0	0.165 (1.8)	0.195 (2.1)	0.23 (2.5)
DI water	1.1 (12.4)	1.265 (13.8)	1.295 (14.0)	1.33 (14.3)
PG	0.5 (5.6)	0.5 (5.4)	0.5 (5.4)	0.5 (5.4)
Methylal	1 (11.3)	1 (10.9). . .		

DETD . . . as described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with DI water. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . .
DETD . . . % g (wt %)

Ketoprofen	2.4	(14.0)	2.4	(14.0)	2.4	(13.9)	2.4 (13.8)		
NaOH	0.6	(3.5)	0.65	(3.8)	0.69	(4.0)	0.73 (4.2)		
DI water	0.6	(3.5)	0.65	(3.8)	0.69	(4.0)	0.73 (4.2)		
Tetraglycol	0.5	(2.9)	0.5	(2.9)	0.5	(2.9)	0.5 (2.9)		
Isopropylmyristate	0.4	(2.3)	0.4	(2.3). . .					
DETD . . .	(32.3)		0.6	(31.6)	0.6	(31.1)			
NaOH	0		0.115	(6.2)	0.135	(7.1)	0.15	(7.8)	
Ethanol	0.4	(24.5)	0.4	(21.5)	0.4	(21.1)	0.4 (20.7)		
DI water	0.6	(36.8)	0.715	(38.4)	0.735	(38.7)	0.75 (38.9)		
HPMCP	0.03	(1.8)	0.03	(1.6)	0.03	(1.6)	0.03	(1.6)	
DETD . . .	(wt %)		g (wt %)						

PPA-HCl	0.5	(6.7)	0.5	(5.7)	0.5	(5.6)	0.5	(5.5)	
Na.sub.2CO.sub.3	0		0.29	(3.3)	0.44	(5.0)	0.74	(8.1)	
DI water	1.0	(13.5)	2.0	(23.0)	2.0	(22.6)	2.0 (21.9)		
Methyl alcohol	0.5	(6.7)	0.5	(5.7)	0.5	(5.6)	0.5	(5.5)	
PG	0.2	(2.7)	0.2. . .						
DETD . . .	(wt %)		g (wt %)						

PPA-HCl	0.5	(6.6)	0.5	(6.1)	0.5	(6.1)	0.5	(6.1)	
K.sub.3PO.sub.4	0		0.57	(7.0)	0.6	(7.3)	0.66	(8.0)	
DI water	1.0	(13.2)	1.0	(12.2)	1.0	(12.2)	1.0	(12.1)	
PG	0.5	(6.6)	0.5	(6.1)	0.5	(6.1)	0.5	(6.1)	
Methyl	0.5	(6.6)	0.5	(6.1). . .					
DETD . . .	(wt %)		g (wt %)						

PPA-HCl	0.5	(6.9)	0.5	(6.4)	0.5	(6.3)	0.5 (6.1)		
K.sub.3PO.sub.4	0		0.57	(7.3)	0.73	(9.2)	1.05 (12.7)		

DI water 1.0 (13.9) 1.0 (12.9) 1.0 (12.6)
1.0 (12.1)
Methyl alcohol 0.5 (6.9) 0.5 (6.4) 0.5 (6.3) 0.5
(6.1)
PG 0.2 (2.8) 0.2. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of
K.sub.3PO.sub.4 that could be dissolved by the small amount of
water on the top of the skin was reduced.
DETD . . . 0.03 (0.5) 0.03 (0.4)
Methyl alcohol 0.5 (8.0) 0.5 (7.8) 0.5 (7.6) 0.5
(7.4)
K.sub.3PO.sub.4 0 0.1 (1.6) 0.3 (4.6) 0.48
(7.1)
DI water 0.5 (8.0) 0.5 (7.8) 0.5 (7.6)
0.5 (7.4)
PG 0.25 (4.0) 0.25 (3.9) 0.25 (3.8) 0.25
(3.7)
PIB adhesive 4 (63.7) 4. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of
K.sub.3PO.sub.4 that could be dissolved by the small amount of
water on the top of the skin was reduced.
DETD . . . (wt %) g (wt %)

Estradiol 0.03 (0.5) 0.03 (0.4) 0.03 (0.4) 0.03 (0.4)
Na.sub.2CO.sub.3 0 0.11 (1.6) 0.3 (4.1) 0.45 (6.1)
DI water 0.5 (8.0) 1.2 (16.9) 1.2 (16.5)
1.2 (16.2)
Methyl alcohol 0.5 (8.0) 0.5 (7.1) 0.5 (6.9) 0.5 (6.7)
PIB adhesive 4 (63.7). . .
DETD . . . to 23.3%. This behavior may be because the amount of
Na.sub.2CO.sub.3 that could be dissolved by the small amount of
water on the top of the skin remained about the same for Est-12,
Est-13 and Est-14.
DETD . . . (wt %) g (wt %)

Estradiol 0.03 (0.5) 0.03 (0.4) 0.03 (0.4) 0.03 (0.4)
MgO 0 0.11 (1.6) 0.3 (4.1) 0.45 (6.1)
DI water 0.5 (8.0) 1.2 (16.9) 1.2 (16.5)
1.2 (16.2)
Methyl alcohol 0.5 (8.0) 0.5 (7.1) 0.5 (6.9) 0.5 (6.7)
PIB adhesive 4 (63.7). . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO
that could be dissolved by the small amount of water on the
top of the skin was reduced.
DETD . . . (wt %) g (wt %)

PPA-HCl 0.5 (6.9) 0.5 (6.0) 0.5 (5.9) 0.5
(5.7)
MgO 0 0.11 (1.3) 0.26 (3.1) 0.50
(5.7)
DI water 1.0 (13.9) 2.0 (24.0) 2.0 (23.6)
2.0 (22.9)
Methyl alcohol 0.5 (6.9) 0.5 (6.0) 0.5 (5.9) 0.5
(5.7)
PG 0.2 (2.8) 0.2. . .
DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO
that could be dissolved by the small amount of water on the
top of the skin was reduced.
DETD . . . Leu-3*
g (wt %) g (wt %) g (wt %)

Leuprolide 0.003 (0.4) 6.4 + 10.sup.-4 (0.18) 6.4 + 10.sup.-4 (0.16)
DI water 0.45 (64.0) 0.28 (80.9) 0.33 (80.3)
NaOH 0 0.0125 (3.6) 0.0275 (6.7)
PG 0.25 (35.6) 0.053 (15.3) 0.053 (13.0)

*Solutions Leu-2 and Leu-3 were prepared using 0.15 g of Leu-1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.

DETD [0363] The cells were filled with DI water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography) to. . . .

DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .

DETD . . . was applied, the donor chamber was covered with parafilm.

TABLE 45

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0369] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . .

DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .

DETD . . . is applied, the donor chamber was covered with parafilm.

TABLE 47

Formulation for the Oxytocin Solution

Ingredient	g
Oxytocin	0.005
DI water	0.6
PG	0.6

DETD [0373] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of oxytocin in the receiver. . .

DETD . . . 0.05 (0.8) 0.1 (1.5)
PIB 4 (61.5) 4 (60.9) 4 (60.6) 4 (59.7)
adhesive

(30%
solid)
Heptane 1 (15.4) 1 (15.2) 1 (15.2) 1 (14.9)
DI water 0 0.035 (0.5) 0.05 (0.8) 0.1 (1.5)
DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in. . .
DETD . . . (13.7) 0.3 (13.50)
PG 0.6 (28.2) 0.6 (27.6) 0.6 (27.4) 0.6 (26.9)
Ethyl alcohol 1 (46.9) 1 (46.1) 1 (45.7) 1 (44.8)
DI water 0.2 (9.4) 0.22 (10.1) 0.23 (10.5) 0.25 (11.2)
HPMC 0.03 (1.4) 0.03 (1.4) 00.3 (1.4) 0.03 (1.3)
NaGH 0 0.02 (0.9) 0.03. . .
DETD . . . from these gels was measured as described in Example 6. Three diffusion cells were used for each formulation. 10% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . .
DETD . . . (7.9) 0.5 (7.8) 0.5 (7.8)
PG 0.5 (7.9) 0.5 (7.9) 0.5 (7.8) 0.5 (7.8)
NaOH 0 0.02 (0.3) 0.04 (0.6) 0.075 (1.2)
DI water 0 0.02 (0.3) 0.04 (0.6) 0.075 (1.2)
PIB adhesive 4 (63.5) 4 (63.1) 4 (62.7) 4 (62.0)
(30% solid)
Heptane 1 (15.9) 1. . .
DETD . . . described in the Methods section. Three diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . .
DETD . . . 0.05 (0.8)
PIB adhesive 4 (61.5) 4 (61.3) 4 (61.2) 4 (60.6)
(30% solid)
Heptane 1 (15.4) 1 (15.3) 1 (15.3) 1 (15.2)
DI water 0 0.01 (0.2) 0.02 (0.3) 0.05 (0.8)
DETD . . . described in the Methods section. Twelve diffusion cells were used for each formulation. The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . .
DETD . . . Solution Weight

	A1-1	A1-2	A1-3
	g (wt %)	g (wt %)	g (wt %)

Alendronate sodium	0.30	(3.2)	0.30	(3.2)	0.30	(3.2)
Glycerin	1.00	(10.8)	1.00	(10.6)	1.00	(10.5)
NaOH	0		0.05	(0.5)	0.10	(1.1)
PIB adhesive (30% solid)	7.5	(80.6)	7.5	(79.8)	7.5	(78.9)
Heptane	0.50	(5.4)	0.50	(5.3)	0.50	(5.3)
DI water	0		0.05	(0.5)	0.10	(1.1)

DETD . . . Film Weight

	Al-1 g (wt %)		Al-2 g (wt %)		Al-3 g (wt %)	
Alendronate sodium	0.30	(8.5)	0.30	(8.3)	0.30	(8.2)
Glycerin	1.00	(28.2)	1.00	(27.8)	1.00	(27.4)
NaOH	0		0.05	(1.4)	0.10	(2.7)
PIB adhesive (30% solid)	2.25	(63.4)	2.25	(62.5)	2.25	(61.6)
Tetraglycol	1.20	(13.5)	1.20	(13.4)	1.20	(13.3)
PIB adhesive (30% solid)	7.00	(78.7)	7.00	(78.0)	7.00	(77.4)
NaOH	0		0.04	(0.4)	0.07	(0.8)
DI water	0		0.04	(0.4)	0.07	(0.8)

DETD . . . (4.4)

DETD . . . Weight

	Pax-1 g (wt %)		Pax-2 g (wt %)		Pax-3 g (wt %)	
Paroxetine HCl	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
DI Water	0.30	(5.1)	0.35	(5.8)	0.40	(6.6)
THF	0.20	(3.4)	0.20	(3.3)	0.20	(3.3)
NaOH	0		0.05	(0.8)	0.10	(1.6)
Benzyl Alcohol	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
Glycerin	0.30	(5.1)	0.30	(5.0)	0.30	(4.9)
PIB adhesive (30% solid)	4.00	(67.8)	4.00	(66.7)	4.00	(65.6)
n-Heptane	0.50	(8.5)	0.50	(8.3)	0.50	(8.2)

DETD . . . (wt %)

Paroxetine HCl	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
NaOH	0		0.05	(2.3)	0.10	(4.5)
Benzyl Alcohol	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
Glycerin	0.30	(14.3)	0.30	(14.0)	0.30	(13.6)
PIB adhesive	1.20	(57.1)	1.20	(55.8)	1.20	(54.5)

DETD . . . measured as described in the Methods section. Three diffusion cells were used for each formulation. The receiver solution, 5% N-methylpyrrolidone/95% water, was completely withdrawn and replaced with fresh receiver solution at each time point. The samples taken were analyzed by an. . .

DETD . . . Weight

	Gala-1 g (wt %)		Gala-2 g (wt %)		Gala-3 g (wt %)	
Galanthamine HBr	0.40	(4.7)	0.40	(4.6)	0.40	(4.6)
DI Water	0.30	(3.5)	0.34	(3.9)	0.38	(4.3)
NaOH	0		0.04	(0.5)	0.08	(0.9)
Glycerin	1.00	(11.6)	1.00	(11.5)	1.00	(11.4)
Benzyl Alcohol	0.40	(4.7)	0.40	(4.6)	0.40	(4.6)
PIB adhesive (30%. . .	6.00	(69.8)	6.00	(69.1)	6.00	(68.5)

DETD . . . (wt %) g (wt %) g (wt %)

Galanthamine HBr	0.40 (11.1)	0.40 (11.0)	0.40 (10.9)

NaOH	0	0.04 (1.1)	0.08 (2.2)
Glycerin	1.00 (27.8)	1.00 (27.5)	1.00 (27.2)
Benzyl Alcohol	0.40 (11.1)	0.40 (11.0)	0.40 (10.9)
PIB adhesive	1.80 (50.0)	1.80 (49.5)	1.80 (48.9)
DETD . . . Weight			

	Hymo-1 g (wt %)	Hymo-2 g (wt %)	Hymo-3 g (wt %)
Hydromorphone HCl	0.20 (2.8)	0.20 (2.7)	0.20 (2.7)
DI Water	0.30 (4.1)	0.38 (5.1)	0.43 (5.7)
NaOH	0	0.08 (1.0)	0.13 (1.7)
Glycerin (16.7)	1.25 (17.2)	1.25 (16.9)	1.25
PIB adhesive (30% solid)	5.00 (69.0)	5.00 (67.6)	4.00 (66.7)
n-Heptane	0.50 (6.9)	0.50 (6.8)	0.50 (6.7)
DETD . . . g (wt %)	g (wt %)	g (wt %)	

Hydromorphone HCl	0.20 (6.8)	0.20 (6.6)	0.20 (6.5)
NaOH	0	0.08 (2.5)	0.13 (4.1)
Glycerin (41.7)	1.25 (42.4)	1.25 (41.3)	1.25
PIB adhesive	1.50 (50.8)	1.50 (49.6)	1.50 (48.8)
DETD . . . g (wt %)	g (wt %)		

Lidocaine	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
PG	0.50 (9.1)	0.50 (8.9)	0.50 (8.8)
Water	0	0.07 (1.2)	0.11 (1.8)
PIB adhesive (30% solid)	4.00 (72.7)	4.00 (70.9)	4.00 (70.1)
NaOH	0	0.07 (1.2)	0.11. . .
DETD . . . %)	g (wt %)	g (wt %)	

Enalapril Maleate	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
PG	0.50 (8.8)	0.50 (8.4)	0.50 (8.1)
DI Water	0.20 (3.5)	0.33 (5.5)	0.45 (7.3)
NaOH	0	0.13 (2.1)	0.25 (4.0)
PIB adhesive (30% solid)	4.00 (70.2)	4.00 (67.2)	4.00 (64.5)
n-Heptane	0.50. . .		

L11 ANSWER 9 OF 10 USPATFULL on STN

ACCESSION NUMBER:	2002:60720 USPATFULL
TITLE:	Dual enhancer composition for topical and transdermal drug delivery
INVENTOR(S):	Hsu, Tsung-Min, San Diego, CA, UNITED STATES Jacobson, Eric C., San Diego, CA, UNITED STATES LoBello, Rose C., San Diego, CA, UNITED STATES Luo, Eric C., Plano, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20020034554	A1	20020321
	US 6582724	B2	20030624
APPLICATION INFO.:	US 2001-972008	A1	20011004 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-738410, filed on 14 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, PENDING Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, PENDING

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 90
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2063
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . to the body surface or may involve use of a drug delivery device. It is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus assist in enhancing the flux of the active agent through a patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD . . . fluid may be natural moisture at the skin surface, or a patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . increases with the value of the Hildebrand solubility parameter. For example, the skin has a σ value of 10, while water has a σ value of 23.4. This in turn means enhancers with solubility parameters of<10 will intervene with the lipid. . .

DETD . . . components of the composition. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

DETD . . . like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. It is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus assist in enhancing the flux of the active agent through a patient's body surface. Thus, the formulation may be aqueous, i.e., contain water, or may be nonaqueous and optionally used in combination with an occlusive overlayer so that moisture evaporating from the body. . .

DETD . . . Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy. . .

DETD [0081] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by

trituration, mechanical mixing, stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridamine, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof.. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . 0.25 g

THF	1.25 g	1.25 g	1.25 g	1.25 g
Beuzyl alcohol	0.7 g	0.7 g	0.7 g	0.7 g
Glycerin	0.7 g	0.7 g	0.7 g	0.7 g
Oleic acid	0	0.2 g	0	0.2 g
Protalan	0.15 g	0.15 g	0.15. . . g	0.3 g
	0.3 g	0.3 g		
Urea	0.2 g	0.2 g	0.2 g	0.2 g
NaOH	0	0.09 g	0.09 g	0
Water	0	0.09 g	0.09 g	0
Testosterone	0.5 g	0.5 g	0.5 g	0.5 g

L11 ANSWER 10 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2001:229217 USPATFULL
TITLE: Hydroxide-releasing agents as skin permeation enhancers
INVENTOR(S): Luo, Eric C., Plano, TX, United States
Jacobson, Eric C., San Diego, CA, United States
Hsu, Tsung-Min, San Diego, CA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20010051166	A1	20011213
	US 6586000	B2	20030701
APPLICATION INFO.:	US 2000-738410	A1	20001214 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000, PENDING Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 91
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 3652
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . the hydroxide-releasing agent prior to transdermal drug administration. Such a solution will generally be comprised of a protic solvent (e.g., water or alcohol) and have a pH in the range of about 8.0 to 13, preferably 8.0 to 11.5, more preferably. . .

SUMM . . . surface or may involve use of a drug delivery device. In either case, it is preferred although not essential that water be present in order for the hydroxide-releasing agent to generate hydroxide ions and thus enhance the flux of the active agent through the patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD [0048] The term "aqueous" refers to a formulation or drug delivery system that contains water or that becomes water -containing following application to the skin or mucosal tissue.

DETD . . . fluid may be natural moisture at the skin surface, or a patch or composition that is used may contain added water, and/or be used in connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably. . .

DETD . . . dicyclomine, diethylproprion, diltiazem, dimenhydrinate, diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline, doxylamine, dypyridame, ephedrine, epinephrine, ethylene diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, lidocaine, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine,. . .

DETD . . . childbearing age or older, in whom ovarian estrogen, progesterone and androgen production has been interrupted either because of natural menopause, surgical procedures, radiation, chemical ovarian ablation or extirpation, or premature ovarian failure. For hormone replacement therapy, and for the other indications. . .

DETD . . . as an ointment, gel, cream, or the like, or may involve use of a drug delivery device. In either case, water must be present in order for the hydroxide-releasing agent to generate hydroxide ions

and thus enhance the flux of the active agent through the patient's body surface. Thus, a formulation or drug reservoir may be aqueous, i.e., contain water, or may be nonaqueous and used in combination with an occlusive overlayer so that moisture evaporating from the body surface. . .

DETD . . . Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy. . .

DETD [0137] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is. . .

DETD . . . and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof.

DETD . . . friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid. . .

DETD . . . components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin;. . .

DETD . . . adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and which should be physically and chemically compatible with the active agent,. . .

DETD . . . permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

DETD . . . are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or

mixture thereof.. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0167] The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by HPLC to determine the concentration of estradiol in the. . .

DETD . . . the patch was measured using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added; the liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

DETD . . . Est-P20

Estradiol	0.0313 g (0.5%)	0.0322 g (0.5%)	0.0308 g (0.5%)
NaOH	0	0.0155 g (0.3%)	0.025 g (0.4%)
DI water	0	0.4155 g (6.9%)	0.425 g (7.0%)
PIB* adhesive (30% solid)	4 g (66.3%)	4 g (66.0%)	4 g (65.8%)

. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD . . . 1.2 g 1.2 g

	(16.7%)	(15.8%)	(15.7%)	(15.7%)
NaOH	0	0.19 g (2.5%)	0.215 g (2.8%)	0.225 g (2.9%)
DI water	0	0.19 g (2.5%)	0.215 g (2.8%)	0.225 g (2.9%)
PIB adhesive	4 g	4 g	4 g	4 g

. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0187] The cells were filled with DI water. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of PPA-HCl in the receiver. . .

DETD . . . 0.75 g 0.75 g

	(8.5%)	(8.2%)	(8.1%)	(8.1%)
NaOH	0	0.165 g (1.8%)	0.195 g (2.1%)	0.23 g (2.5%)
DI water	1.1 g (12.4%)	1.265 g (13.8%)	1.295 g (14.0%)	1.33 g (14.3%)
Propylene	0.5 g	0.5 g	0.5 g	0.5. . .

DETD . . . formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other

solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was cut. . .

DETD . . . 2.4 g				
	(14.0%)	(14.0%)	(13.9%)	(13.8%)
NaOH	0.6 g	0.65 g	0.69 g	0.73 g
	(3.5%)	(3.8%)	(4.0%)	(4.2%)
DI water	0.6 g	0.65 g	0.69 g	0.73 g
	(3.5%)	(3.8%)	(4.0%)	(4.2%)
PIB adhesive	8 g	8 g	8 g. . .	
DETD . . . g	0.4 g	0.4 g	0.4 g	
	(24.5%)	(21.5%)	(21.1%)	(20.7%)
DI	0.6 g	0.715 g	0.735 g	0.75 g
Water	(36.8%)	(38.4%)	(38.7%)	(38.9%)
HPMCP*	0.03 g	0.03 g	0.03 g	0.03 g
	(1.8%)	(1.6%)	(1.6%)	(1.6%)

*HPMCP Hydroxypropyl methyl cellulose. . .

DETD . . .	0.5 g	0.5 g	0.5 g	
	(6.7%)	(5.7%)	(5.6%)	(5.5%)
Na.sub.2CO.sub.3 0		0.29 g	0.44 g	0.74 g
		(3.3%)	(5.0%)	(8.1%)
DI water	1.0 g	2.0 g	2.0 g	2.0 g
	(13.5%)	(23.0%)	(22.6%)	(21.9%)
Methyl alcohol. . .	0.5 g	0.5 g	0.5 g	0.5 g
DETD . . .	0.5 g	0.5 g	0.5 g	
	(6.6%)	(6.1%)	(6.1%)	(6.1%)
K.sub.3PO.sub.4 0		0.57 g	0.6 g	0.66 g
		(7.0%)	(7.3%)	(8.0%)
DI water	1.0 g	1.0 g	1.0 g	1.0 g
	(13.2%)	(12.2%)	(12.2%)	(12.1%)
Propylene glycol. . .	0.5 g	0.5 g	0.5 g	0.5 g
DETD . . .	(6.9%)	0.5 g	0.5 g	0.5 g (6.1%)
		(6.4%)	(6.3%)	
K.sub.3PO.sub.4 0		0.57 g	0.73 g	1.05 g
		(7.3%)	(9.2%)	(12.7%)
DI water	1.0 g	1.0 g	1.0 g	1.0 g
	(13.9%)	(12.9%)	(12.6%)	(12.1%)
Methyl	0.5 g (6.9%)	0.5 g	0.5 g	0.5. . .

DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD . . . g	(7.6%)	0.5 g		
alcohol	(8.0%)	(7.8%)		(7.4%)
K.sub.3PO.sub.4 0		0.1 g	0.3 g (4.6%)	0.48 g
		(1.6%)		(7.1%)
DI water	0.5 g	0.5 g	0.5 g (7.6%)	0.5 g
	(8.0%)	(7.8%)		(7.4%)
Propylene	0.25 g	0.25 g	0.25 g (3.8%). . .	

DETD . . . made the adhesive matrix more hydrophobic and the amount of K.sub.3PO.sub.4 that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD . . .	0.03 g	0.03 g	0.03 g	
	(0.5%)	(0.4%)	(0.4%)	(0.4%)
Na.sub.2CO.sub.3 0		0.11 g	0.3 g	0.45 g
		(1.6%)	(4.1%)	(6.1%)
DI water	0.5g	1.2g	1.2g	1.2g
	(8.0%)	(16.9%)	(16.5%)	(16.2%)

Methyl alcohol PIB. . .	0.5 g (8.0%)	0.5 g (7.1%)	0.5 g (6.9%)	0.5 g (6.7%)

DETD . . . and 34). This behavior may be because the amount of Na.sub.2CO.sub.3 that could be dissolved by the small amount of water on the top of the skin remained about the same for Est-PC2, Est-PC3 and Est-PC4.

DETD . . .	0.03 g (0.5%)	0.03 g (0.4%)	0.03 g (0.4%)	(0.4%)
MgO	0	0.11 g (1.6%)	0.3 g (4.1%)	0.45 g (6.1%)
DI water	0.5 g (8.0%)	1.2 g (16.9%)	1.2 g (16.5%)	1.2 g (16.2%)
Methyl alcohol. . .	0.5 g	0.5 g	0.5 g	0.5 g

DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD . . .	0.5 g (6.9%)	0.5 g (6.0%)	0.5 g (5.9%)	(5.7%)
MgO	0	0.11 g (1.3%)	0.26 g (3.1%)	0.50 g (5.7%)
DI water	1.0 g (13.9%)	2.0 g (24.0%)	2.0 g (23.6%)	2.0 g (22.9%)
Methyl alcohol. . .	0.5 g	0.5 g	0.5 g	0.5 g

DETD . . . made the adhesive matrix more hydrophobic and the amount of MgO that could be dissolved by the small amount of water on the top of the skin was reduced.

DETD [0294] The cells were filled with deionized (DI) water for a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. Samples of the receiver solution were taken and analyzed by HPLC (high pressure liquid chromatography) to. . . Systems

	Leu-S1	Leu-S2*	Leu-S3*
Leuprolide 10.sup.-4 g	0.003 g (0.4%)	6.4 + 10.sup.-4 g (0.18%)	6.4 g + (0.16%)
DI water	0.45 g (64.0%)	0.28 g (80.9%)	0.33 g (80.3%)
NaOH	0 g (0.0%)	0.0125 g (3.6%)	0.0275 g (6.7%)
Propylene. . .	(13.0%)		

*Solutions Leu:S2 and Leu-3 were prepared using 0.15 g of Leu-S1, then adding the correct amount of NaOH and DI water. Percentages may not add up to 100% due to rounding.

DETD . . . with 4% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .

DETD [0300] The cells were filled with DI water as a receiver solution. The DI water had been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by HPLC for the concentration of oxytocin in the receiver solution.. . . for each time point, which were listed in Table 46.

TABLE 45

Formulation for the Oxytocin Solution

	Oxytocin	0.005	g
	DI water	0.6	g
	Propylene Glycol	0.6	g

DETD . . . with 1.0% NaOH solution. To wash away the NaOH solution, the receiving fluid was removed and replaced with fresh DI water. This was done twice. DI water was added to the donor chamber to dilute the NaOH solution and then the donor solution was removed. This was. . .

DETD [0304] The cells were filled with DI water as a receiver solution. The DI water has been degased to remove air bubbles. The receiver solution was completely withdrawn and replaced with fresh DI water at each time point. The samples taken were analyzed by an HPLC for the concentration of oxytocin in the receiver. . . for each time point, which were listed in Table 48.

TABLE 47

Formulation for the Oxytocin Solution

	Oxytocin	0.005	g
	DI water	0.6	g
	Propylene Glycol	0.6	g

DETD . . . Each formulation was coated on a release liner and dried in an oven at 55EC for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0308] The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in. . .

DETD . . . of the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water /patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discard. The vial. . .

DETD . . . 4 g 4 g

solid)	(61.5%)	(60.9%)	(60.6%)	(59.7%)
Heptane	1 g	1 g	1 g	1 g
	(15.4%)	(15.2%)	(15.2%)	(14.9%)
DI water	0	0.035 g	0.05 g	0.1 g
		(0.5%)	(0.8%)	(1.5%)

DETD [0319] 10% ethanol/90% water solution was used as the receiver solution. The volume of receiver solution was 8 ml. The receiver solution was collected and replaced with fresh ethanol/water solution at each time point. The receiver solution collected was analyzed by an HPLC for the concentration of diclofenac sodium.. . .

DETD . . . g 0.6 g

glycol	(28.2%)	(27.6%)	(27.4%)	(26.9%)
Ethyl alcohol	1 g (46.9%)	1 g (46.1%)	1 g	1 g

				(45.7%)	(44.8%)
DI	water	0.2 g	0.22 g	0.23 g	0.25 g
		(9.4%)	(10.1%)	(10.5%)	(11.2%)
HPMC		0.03 g	0.03 g	00.3 g	0.03 g

. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0326] The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of testosterone in the. . . .

DETD . . . the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water /patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

DETD . . . 0.5 g (7.9%)	0.5 g (7.8%)	0.5 g (7.8%)		
glycol	(7.9%)			
NaOH	0	0.02 g (0.3%)	0.04 g (0.6%)	0.075 g (1.2%)
DI water (1.2%)	0	0.02 g (0.3%)	0.04 g (0.6%)	0.075 g
PIB adhesive	4 g	4 g (63.1%)	4 g (62.7%)	4. . .

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0337] The cells were filled with 10% ethanol/90% water solution. The receiver solution was completely withdrawn and replaced with fresh ethanol/water solution at each time point. The samples taken were analyzed by an HPLC for the concentration of oxybutynin HCl in. . . Solution Weight) for

Three Oxybutynin HCl Transdermal Systems

	Oxy-P1	Oxy-P2	Oxy-P3
Oxybutynin HCl	0.5 g (6.5%)	0.5 g (6.3%)	0.5 g (6.2%)
DI water	0.65 g (8.4%)	0.75 g (9.5%) (10.5%)	0.85 g
NaOH	0.15 g (1.9%)	0.25 g (3.2%)	0.35 g (4.3%)
Propylene glycol	0.3. . . .		

DETD . . . formulation was coated on a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then. . .

DETD [0343] The cells were filled with 10% ethanol/90% water solution. At each time point, the pH at the interface between skin and the patch for three diffusion cells was. . . interface were listed in Table 65. For all other cells, the receiving fluid was completely withdrawn and replaced with fresh ethanol/water solution. The samples taken were analyzed by an HPLC for the concentration of diclofenac sodium in the receiver solution. The. . .

DETD . . . the patch was determined using the following procedures. A 2.5 cm.sup.2 circular patch was punched out. Ten ml of purified water was pipetted into a glass vial, and a stir bar was added, the liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial. . .

	4 g (61.2%)	4 g (60.6%)		
(30% solid)		(61.3%)		
Heptane	1 g (15.4%)	1 g (15.3%)	1 g (15.3%)	1 g (15.2%)
DI water	0	0.01 g (0.2%)	0.02 g (0.3%)	0.05 g (0.8%)